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NEUROPATHOLOGICAL PAPERS

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NEUROPATHOLOGICAL PAPERS.

CONTENTS.

I. The Neuroglia Framework of the Cerebellum in Cases of Marginal Sclerosis.
E. E. Southard.
(From the Journal of Medical Research, xiii, 5, August, 1905.)

II. A Case of Cholesterin Stones in the Brain and Cord.
E. E. Southard.
(From the Journal of the American Medical Association, December 2, 1905.)

III. A Case of Pott's Disease in the Monkey.
E. E. Southard.
(From the Journal of Medical Research, xiv, 2, January, 1906.)

IV. Cystic Aplasia of the Cerebral Hemispheres in an Idiot Child.
W. N. Bullard and E. E. Southard.
(From the Journal of Medical Research, xiv, 2, January, 1906.)

V. Diffuse Gliosis of the Cerebral White Matter in a Child.
W. N. Bullard and E. E. Southard.
(From the Journal of Nervous and Mental Disease, January, 1906.)

VI. A Study of Brain Infections with the Pneumococcus.
E. E. Southard and C. W. Keene.
(From the Journal of the American Medical Association, January 6, 1906.)

VII. Cerebral Seizures with Suboccipital Pain: Miliary Cerebral and Gross Vertebral Aneurysms.
W. D. Ruston and E. E. Southard.
(From the Boston Medical and Surgical Journal, cliv, 12, March 22, 1906.)

VIII. A Case of Glioma of the Frontal Lobe with Invasion of the Opposite Hemisphere.
E. E. Southard.
(From the American Journal of Insanity, lxii, 4, April, 1906.)

NOTE.

The papers here bound together form part of the work in neuropathology in the Harvard Medical School during 1905. As in 1904, the work has been made possible by the Bullard gifts and by donations from the fund established by the late Arthur W. Blake. The work was done chiefly in the laboratory of the Boston City Hospital, under the direction of Professors W. T. Councilman and F. B. Mallory, and will be continued, under the Bullard Professorship of Neuropathology established in March, 1906, in the laboratories of the Danvers Insane Hospital and the new Harvard Medical School. E. E. S.

THE NEUROGLIA FRAMEWORK OF THE CEREBELLUM IN CASES OF MARGINAL SCLEROSIS

E. E. SOUTHARD, M.D.

(Instructor in Neuropathology and Charles Eliot Ware Fellow, Harvard University Medical School)

(From the Pathological Laboratory of the Boston City Hospital)

Reprinted from

The Journal of Medical Research, Volume XIII., No. 5

(New Series, Vol. VIII., No. 5), pp. 487-498, August, 1905

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THE NEUROGLIA FRAMEWORK OF THE CEREBELLUM IN CASES OF MARGINAL SCLEROSIS.[1]

E. E. SOUTHARD, M.D.

(*Instructor in Neuropathology and Charles Eliot Ware Fellow, Harvard University Medical School.*)

(*From the Pathological Laboratory of the Boston City Hospital.*)

I. MATERIAL.

Dominant views of the neuroglia framework of the cerebellum are derived from Golgi studies. The data of the Golgi pictures in the cerebellum, as elsewhere in the central nervous system, fail to coincide in some respects with the data of the differential methods for neuroglia fibrils. The stained objects which the Golgi method demonstrates as glia cell-processes turn out with differential methods to be intercellular fibrils resembling the types of fibril developed between connective tissue cells. The distinction in the case of neuroglia tissue is of historic importance by reason of the bizarre claims that the alleged cell-processes are retractile organs having perhaps to do with sundry nerve functions. The present study is an incident of the old controversy with respect to the fibrils.

I have here sought to develop and modify the dominant view of cerebellar structure by a resort to adult tissue examined with Mallory's phosphotungstic acid hematein method for neuroglia fibrils. This method has proved satisfactory in paraffin sections of tissue fixed in Zenker's fluid.[2] Well preserved tissue from thirty-five brains has been employed for this study, including cases of marginal sclerosis due to trauma, old age, and ischemia, cases of early neuroglia reaction in pyogenic and tuberculous meningitis, and various almost normal material.

Attention was first drawn to the problem by the delicate though well-defined reaction of the cerebellar neuroglia in cases of tuberculous leptomeningitis. Herein the characteristic radial fibers of the molecular layer, the fibers long known as Bergmann's fibers, are brought out in places with diagrammatic clearness (Fig. 7). The problem of the origin and relations of Bergmann's fibers and of other fibrils, both in the molecular layer and in the internal layers of the cerebellar lamina, was brought sharply to mind, however, by findings in a case of syphilis.

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[1] Read at the Fifth Annual Meeting of the American Association of Pathologists and Bacteriologists, held in Chicago, April, 1905. Received for publication May 14, 1905.

[2] F. B. Mallory. A Contribution to the Classification of Tumors. Journal of Medical Research, xiii, 2, January, 1905, Method 4, p. 116.

I shall therefore, first, present an account of the maximal sclerosis found in a case of syphilis; secondly, bring out the common elements in this and other cases of cerebellar lesion and in the normal cerebellum; and, thirdly, describe the neuroglia fibril systems peculiar to the cerebellum, with particular reference to the origin and relations of the fibers called Bergmann's fibers.

II. FINDINGS IN A CASE OF SYPHILIS.

Following is a sketch of the total picture in a case showing complete laminar sclerosis:

Age 39 years. — Slender woman of middle height, with extensive sacral bed-sores, open ulcers of feet, and brown macules on abdomen.

Vascular System. — Heart muscle slightly fatty. Ridged and slightly puckered aortitis without atheroma of ascending arch of aorta. Right vertebral artery reduced to a thread, left shows ridge of sclerosis. Carotid arteries slightly stiff. Pulmonary arteries near origin show faint traces of sclerosis.

Small infarcts of lung.

Multiple infarcts of adrenals (made out first microscopically).

Symmetrical destructive and atrophic lesions of gray matter of corpora striata with atrophy of anterior segments of internal capsules.

Destructive lesion of amygdala and biventral lobule of left hemisphere of cerebellum.

Minute foci of red softening in various portions of cortex cerebri and anterior horns of lumbar cord.

Atrophy of cortex of cerebrum, cerebellum, and spinal cord. Notable induration of forceps minor and tapetum, gray degeneration of long tracts in spinal cord, atrophy of fibers of cauda equina.

Chronic diffuse leptomeningitis, notably of vertex, base and thoracic portion of cord.

Atrophy of right third and sixth, left seventh and eighth, and sensory root of left fifth cranial nerves.

Fatty liver and right kidney.

Left sided hydronephrosis with dilatation of ureter (no cicatrix or other obstruction made out).

To this summary may be added a description of the gross findings in the cerebellum. The marginal convolutions of the cerebellum show thinning of cortical substance, best marked near superior vermis and along posterior notch. The outer portion of the amygdala and inner portion of the biventral lobule on the left side show a destructive lesion with depression 1.5 centimeters in diameter by .5–.75 centimeter in depth. The depression is lined by brownish moist pia mater, dipping gradually down from the surrounding marginal convolutions which show a well-marked cortical atrophy. The lesion on section resembles roughly the destructive lesions of the basal ganglia and shows effacement of normal markings and a smoothly cutting jelly-like brown substance, here and there yellowed and slightly opaque.

To sum up, the subject shows (1) focal disease of the arteries, with destructive lesions in several organs due to arterial occlusion, (2) extensive chronic cerebrospinal leptomeningitis, (3) various atrophies in the nervous system, one group secondary to destructive lesions interrupting nerve tracts, another group due to leptomeningitis, and a group of obscure origin.

We are here particularly concerned with the cerebellar lesions.

The focal lesion in the cerebellum is an old cyst of softening. The smoothly undulating walls are composed of densely fibrillar neuroglia. The interior consists of numerous capillaries with loose fibrous coats and surrounding spaces which contain fibrin, albumen coagulum, and great numbers of swollen cells enclosing granular pigment. Similar cells are dotted throughout the wall in small spaces, which give the tissue a sieve-like appearance in cross section. The intrinsic glia cells in the cyst wall are few and inactive. The fibrils are fine and of even diameters, although where they abut upon or make out into the cyst they may become coarse agglutinated masses.

Some of the laminæ of the cerebellum, especially the marginal gyri and the gyri around the cyst of softening, show a loss of substance which is peculiar (Figs. 6 and 13). The contour and stratification of the affected laminæ remain, but the component tissues have undergone a differential loss of substance. The nerve elements have been lost. The white core contains no myelinated fibers. The Purkinje cells and their appertaining dendrites are absent. The layer of small nerve cells known as granules is represented only by a layer of neuroglia cells The remnant of the inner or granule layer, with its dense felt-work of neuroglia, serves to maintain the contour and suggests the stratification of the normal cerebellar cortex. Radiating out from the modified inner layer are bundles of coarse neuroglia fibrils which, in situation at least, recall the fibers called Bergmann's fibers. Among these fibers there occur for wide areas no cell-bodies whatever. In many cases the bundles can be demonstrated to run all the way from the pia mater, where they may spread out to imitate a foot (Fig. 11), to the neighborhood of the cells of the granule layer, which cells the fibrillæ embrace in the characteristic fashion of neuroglia tissue. The nuclei of the cells related with these radial fibrillæ are large, oval vesicular, and provided with numerous chromatin dots; cell-bodies are rarely visible. Similar cells stand in similar relation to numerous finer fibrillæ which run concentrically about as a kind of central beam for the granule layer. A third series of fine fibers runs at right angles to the two preceding, is derived from similar cells, and occupies the locus of the Purkinje cell layer. The tissue replacing the central core is composed of numerous fibrillæ running in many directions, together with their cells of origin and a few vessels. In some laminæ the impression is gained that fibers similar to Bergmann's fibers, or continuous with them, radiate inwards from the granule layer, but the core fibers are so abundant often as to obscure this picture.

It might be urged that so striking a picture is due to aplasia rather than destruction of the nerve cells. In certain laminæ, however, groups of the characteristic nerve cells of the granule layer are seen, and among them examples of chromophilic cells in the process of necrosis. Necrotic Purkinje cells are occasionally demonstrable.

Further evidence of the progressive character of the changes is to be found in a second group of altered laminae. In these laminæ the same general relations hold, but the fibril reaction is more compact. The fibrils occupying the locus of Bergmann's fibers are still chiefly radial, but they almost completely pack the old molecular layer. There are a few more neuroglia nuclei in the molecular layer than in the laminæ first described. Nevertheless, the greater number of fibrillæ are derived from the neuroglia cells of the granule layer. The nuclei of these cells are slightly smaller than those of the same layer in the laminæ of the first group. In these laminæ with the denser gliosis there are more examples of granule nerve cells preserved.

III. REACTION OF CEREBELLAR TISSUES TO INJURY.

There are certain elements held in common by the reaction in the case detailed above and the reactions on the part of the cerebellum in other and various conditions. A sketch of the total activity of the neuroglia in the cerebellum is obtained by comparing the maximal process shown above with lesser degrees and earlier stages of the reaction shown in other cases of ischemia, in trauma, and in bacterial infection.

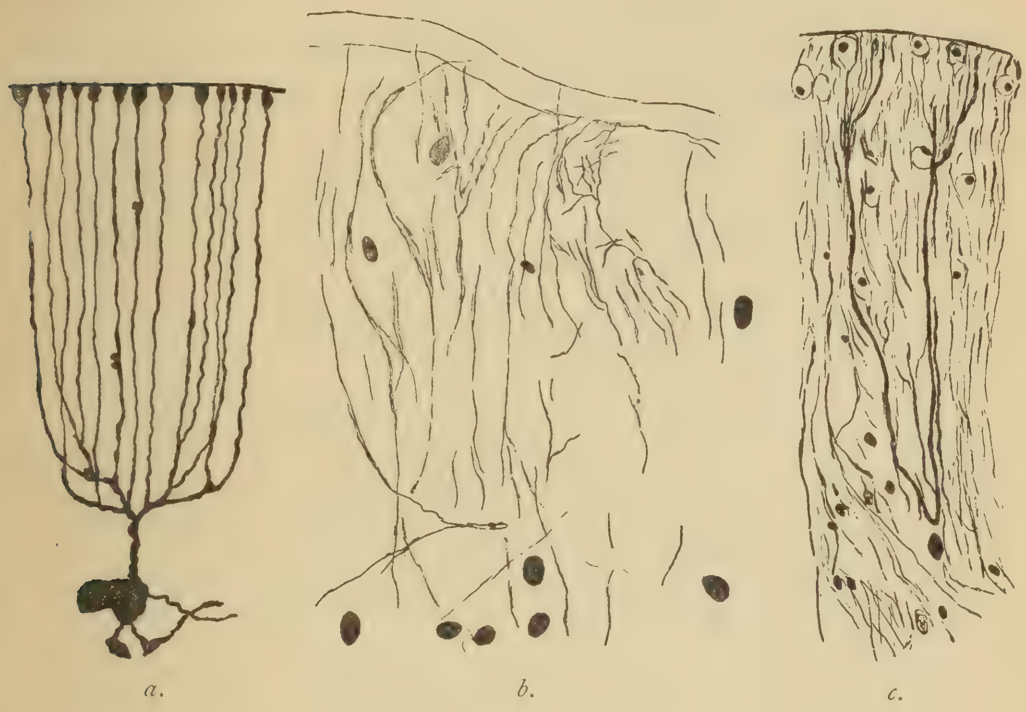
The neuroglia reaction of the medullary center in the cases examined has been homogeneous and almost regular. Upon degeneration of axones and myelin sheaths, the neuroglia cells become active in situ and pass through the usual changes leading to new fibril formation. The fibrils in the developing as in the finished process are governed by no rule as to direction, except that, in the immediate neighborhood of vessels, the fibrils are developed in some quantity and may assume a radial relation to the adventitiæ. The amount of fibrillary gliosis is roughly proportional to the amount of neuroglia present normally in the reacting region. Since there are more neuroglia cells in the medullary center than in the granular layer (or because they are less capable of fibril-production in the denser granular layer), the picture is sometimes produced of a vessel midway between the two zones with a deep fibrillary gliosis on the side toward the medullary center and little or no reaction on the side toward the granular layer (Fig. 1).

The neuroglia reaction of the granular layer is almost regular, but is no longer homogeneous, since in this layer there is already shown a tendency to parallelism of fibrils, which roof in the medullary center and embrace it so as to be demonstrated lengthwise in a cross section of the lamina. The earliest phases of the process show little more than a homogeneous sprinkling of neuroglia cells like those of the medullary center. There is no marked tendency to production of fibrils until many of the granule nerve cells have been lost. In a case of epilepsy in a youth, numerous fibrils were discovered in the granular layer without notable destruction or alteration of the granule nerve cells. Fibrils seem to be overproduced at times also about cells of the gray matter of the dentate nucleus, although the nerve cells show little change.

The neuroglia reaction of the granular layer cannot well be considered apart from the reaction of the other marginal layers, as may be surmised from the inter-relation of fibril masses described in the case of syphilis.

The common element in the neuroglia reaction, as shown in the marginal layers of the lamina, seems to be the reaction in and alongside the Purkinje cell layer. The Purkinje cell layer is a *locus minoris resistentiæ*. The macerating cerebellum in edema tends to split along this layer (Figs. 2 and 3). In tuberculous meningitis and in epidemic cerebrospinal meningitis there is often considerable cell-débris and edema in the layer. In tuberculous meningitis focal destruction of Purkinje cells and loosening of structures in the layer are not seldom found. In ischemic injury to a lamina a line of neuroglia cells in this layer may be the only sign of reaction for a considerable distance on either side of the layer (Figs. 3 and 4).

The neuroglia cells in this layer produce fibrils whose direction is characteristic. The foci in tuberculous meningitis show that the earliest reaction upon injury to the layer is a change in the neuroglia cells therein, such that numerous radial fibrils are thrown out toward the pia mater (Fig. 7). This development of numerous radial fibrils antedates the development of cross fibrils, and the radial fibrils remain as a rule coarser than the cross fibrils. The disposition of the radial fibrils in foci where Purkinje cell-processes still exist indicates that their direction may be set by the direction of the Purkinje cell-processes, along which they may be seen to run sometimes normally. The effect of



TEXT FIG. 1.

a. Golgi-picture of neuroglia-cell, processes, and feet (child of three months). From G. Retzius, Biol. Unters., N.F., Bd. vi, No. 1. 1894. Tafel xi, Fig. 4.

b. Molecular layer of cerebellum (Weigert's neuroglia stain). From C. Weigert, Beiträge zur Kenntnis der normalen menschlichen Neuroglia, 1895. Tafel ix, Fig. 5.

c. Molecular layer of cerebellum (Mallory's phosphotungstic acid hematein method after fixation in Zenker's fluid). Compare also Plate XXXVII., Fig. 7.

these numerous parallel fibrils is to keep the marginal layers from over-riding.

The tendency to extensive development of radial fibrils is a frequent element in all sorts of cerebellar lesions, in trauma, ischemia, atrophy, and bacterial infection. The fibrils are demonstrable in the normal cerebellum. They have had a various history. Seen by Bergmann and called by him a network, they were rediscovered by v. Kupffer, who described them as independent fibers, but regarded them as nerve fibers. The Golgi workers picture them as broom-like collections of fibers derived by multiple branching from a neuroglia cell of the inner layers. Weigert pictures them as independent fibrils, but was apparently unable with his material to make out their cells of origin.[1]

IV. THE GLIA FIBRIL SYSTEMS IN THE SCLEROTIC CEREBELLUM.

There are three sets of neuroglia fibrils in a thoroughly sclerotic lamina of the cerebellum (Figs. 10, 11, and 12). These sets of fibrils intersect each other at approximately right angles. The fibril masses so arranged form a kind of beam work, which maintains the contour of the lamina in a mechanical fashion.

Of these fibrils the most constant, prominent, and mechanically effective set is the radial system. This system is found massively developed in places in the case of syphilis (Figs. 6 and 13) and throughout sclerotic laminæ in the case of a boy of four and a half years with cerebellar lesions of unknown origin and giving no clinical sign[2] (Figs. 2 and 8).

The cells of origin of the radial fibrils (Bergmann's fibers) are well shown in certain foci of Purkinje cell destruction in tuberculous leptomeningitis (Fig. 7). The persistence of these neuroglia cells as a definite new-formed layer along the old line of Purkinje cells is well shown in certain small sharp-edged foci of nerve cell devastation of ischemic origin (case of syphilis) (Figs. 3 and 4). It is clear that, whatever their mechanical effect against stress, the fibrils develop from preëxistent cells. These cells multiply to some extent, and the appertaining fibrils are developed along the line of least resistance among the dying processes of the Purkinje cells.

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[1] C. Weigert. Beiträge zur Kenntnis der normalen menschlichen Neuroglia, 1895, S. 170.

[2] The tissues in this case were kindly given me by Dr. F. B. Mallory, and the clinical history was communicated by Dr. W. N. Bullard from the Children's Hospital records.

The two concentric fibril systems are developed at right angles to the system of Bergmann's fibers. The concentric systems are less constant and prominent than the radial system. In early stages of sclerosis numerous cross fibrils are seen far out in the molecular layer or even completely filling the molecular layer, forming a lattice work with the radial fibrils (Fig. 5). Moreover, at the periphery of sclerotic lesions, dense gliosis may occur, formed of fibrils running for the most part in three planes at right angles to one another (Fig. 9). In the older stages of sclerosis, however, whether through contraction along the stout Bergmann fibers as if along taut wires, or for some unknown reason, the concentric systems are limited more especially to the inner zones; the inner concentric layer occupying the outer portion of the former granule layer and the outer concentric layer occupying the locus of the old basket-cell layer of the Golgi pictures (Figs. 10, 11, and 12). In cross sections of a lamina the outer concentric layer of fibrils is the least prominent, because these fibrils are themselves cut in cross section and appear as a fine powdery belt. For some reason this powdery belt in some of the older lesions appears split into two zones, the narrower of which interpenetrates the outer part of the radial system a short distance from the pia mater (Figs. 13 and 14).

It is not so easy to demonstrate the cells of origin for the concentric fibril systems as those for the fibers of Bergmann, since these finer fibrils can scarcely be recognized as occurring in zones until they are already developed in quantity. Nevertheless, there can be no doubt that they are developed from cells in or near the old Purkinje cell layer. Why these fibrils take the course they do will be found in the examination of tissues showing early and differential cell destruction in the inner layers, giving rise to glia overgrowth along certain lines only. For the present it is enough to call attention to their course and to the resistance against stress which, together with the radial fibers, they offer.

Between the fibrils, which in the outer part of the former molecular layer may be widely spaced, there is a substance which fails to stain by the methods used and consists of minute ringed or reticular material, optically demonstrable. In some places the Bergmann fibers appear to have at last given way, and the neuroglia tissue of one side of the lamina may contract into a tight mesh in the locus of the cells of origin of Bergmann's fibers (Figs. 13 and 15).

The best demonstration of these relations is afforded by a lesion severe enough to destroy the nerve cells, and not severe enough to affect the connective tissues. Such a lesion permits unusual activity of the neuroglia cells, perhaps because there is more room for it (to adopt the Weigert line of thought).[1]

V. SUMMARY.

The tissues of the human cerebellum show characteristic reactions to injury. There is a line of cleavage in the normal, and especially in the macerating cerebellum, in the layer known as the layer of Purkinje cells. The cells of this layer suffer the maximum injury both upon impairment of blood supply and in acute diseases like tuberculous and pyogenic leptomeningitis. The death of the Purkinje cells is attended with a loss of their processes, so that the outer or molecular layer also tends to break down Severer injury destroys not only the Purkinje cells, but also the nerve cells known as the granules of the inner or granular layer. Throughout the varying degrees of such injury cells of the neuroglia series persist. Neuroglia cells are found active in foci which contain no nerve cells.

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[1] C. Weigert. Neue Fragestellungen in der pathologischen Anatomie, Deutsche med. Wchnschr., 1896, xxii, 635–640.

The neuroglia reaction differs characteristically in the various layers making up a lamina. In the medullary center there is a regular and homogeneous gliosis, in which the preëxistent cells produce fibrils which run in no given directions and form a felt-work. In the other layers the neuroglia reaction is regular, but is not homogeneous.

The neuroglia reaction of the marginal layers is such that a quite regular stratification is preserved. The strata of a sclerotic lamina are formed of fibrils running in fairly definite directions. The former line of cleavage is replaced with a line of cells which produce numerous fibrils forming three layers — (1) a layer of fine fibrils lying flatwise to the outer limits of the medullary center, (2) a layer of fine fibrils external and at right angles to these and also lying flatwise with relation to the medullary center, and (3) a layer composed of coarser radial fibrils running, vertically with respect to the medullary center, out to the connective tissue of the pia mater. Of these fibril systems, the first to develop is the mass of radial fibrils known as Bergmann's fibers. It is now possible to doubt the accuracy of Golgi pictures, which make these fibers branch from cells of the inner layers. Their true cells of origin lie along the line of cleavage in a cerebellar lamina.

(I wish to thank Profs. W. T. Councilman and F. B. Mallory for aid in the work.)

DESCRIPTION OF PLATES.

PLATE XXXVI.

FIG. 1. — Fibrillary overgrowth of neuroglia around a vessel lying between the medullary center and the granular layer. Reaction more marked on the side toward the medullary center (from a case of surgical trauma). x 250.

FIG. 2. — Marginal sclerosis in a boy of four and one-half years. Note the tendency to artificial splitting in the normal laminæ along the line of junction between granular and molecular layers.

FIG. 3. — Laminæ showing lesions the result of ischemia (case of syphilis). Focal devastation of Purkinje cells and granule cells. Note tendency to split along the Purkinje cell layer in the more normal parts and the absence of splitting in the region of nerve cell destruction.

FIG. 4.— Detail from Fig. 3. On the left, destruction of granule cells of granule layer with persistence of neuroglia cells. In the middle a belt of

neuroglia cells has been developed in the locus of the destroyed Purkinje cell layer. x 190.

Fig. 5. — Dense gliosis in molecular layer in early fibrillary stage at bottom of sulcus. Tendency to deposit of fibrils at right angles (case of syphilis). x 190.

Fig. 6. — Advanced gliosis of a lamina (case of syphilis). The densest portion of the lamina is in the locus of the former layer of Purkinje cells. Radiating out from the dense portion are fibrils running to pia mater and fibrils running toward the destroyed medullary center. Contour of lamina maintained.

Plate XXXVII.

Fig. 7.— The molecular layer and a portion of the granular layer from a focus in tuberculous leptomeningitis. In the focus the Purkinje cells have become destroyed, but the locus of the Purkinje cell layer is indicated by a belt of neuroglia cells, about which is going on active fibril production. The radial fibrils (Bergmann's fibers) run out to the pia, but cannot be demonstrated far in the granular layer. A belt of fibrils at right angles with Bergmann's fibers can be faintly seen internal to the belt of neuroglia cells.

Fig. 8.— Detail from Fig. 2. Sclerotic lamina, showing radiate appearance of molecular layer, due to overproduction of Bergmann's fibers. Their cells of origin appear as a dark belt in the locus of the Purkinje cell layer. There is no longer evidence of Purkinje cell layer, granular layer, or medullary center, despite the maintenance of contour and stratification.

Fig. 9. — Border of lesion (case of syphilis). Tendency to lattice-like arrangement of fibrils to left.

Fig. 10.—To demonstrate the outer concentric system of fibrils (powdery belt) cut across. x 500.

Plate XXXVIII.

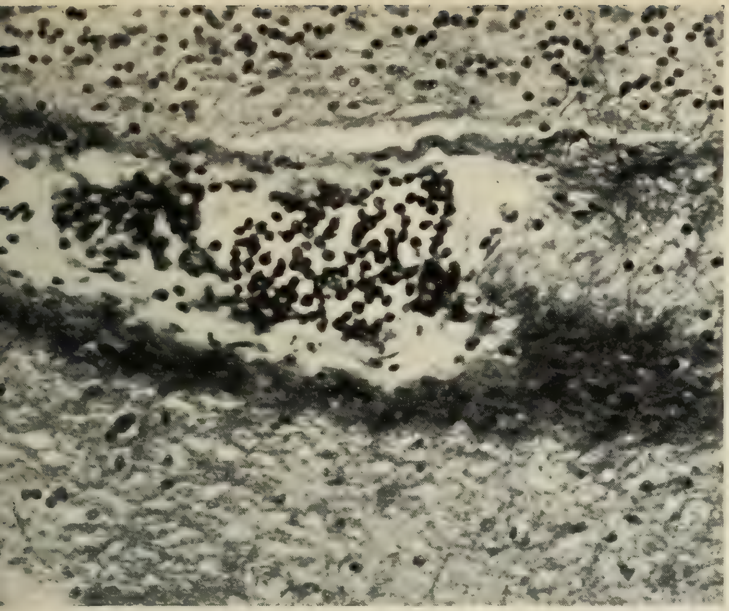
Fig. 11. — Fibril systems in outer layers of sclerotic lamina (case of syphilis). Radial fibers well marked. At the line of attachment with the pia mater, the fibrils often spread out to imitate the feet of the Golgi pictures.

Fig. 12. — Fibril systems in outer layers of sclerotic lamina (case of syphilis). Radial fibers best marked about small vessel. Middle zone shows the outer concentric system of fibrils cut in cross section to form powdery belt. Between this cross-cut fibril system and the inner concentric system is a belt of neuroglia nuclei.

Fig. 13. — Laminæ to show the occasional division of the outer concentric fibril system (powdery belt) into two portions. The right side of the lamina upon the right shows the dense mesh, which is the most advanced stage of sclerosis in the lamina.

Fig. 14. — Detail to show division of outer concentric fibril system. x 190.

Fig. 15. — Detail from Fig. 13 to show dense mesh in the locus of the old Purkinje cell layer in advanced sclerosis. x 190.



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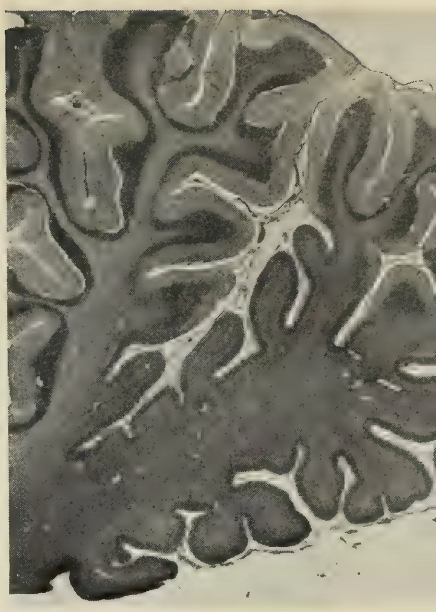

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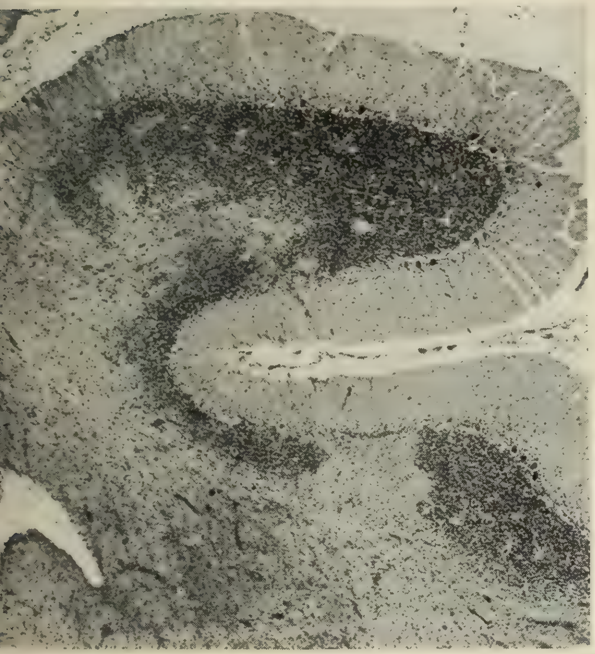

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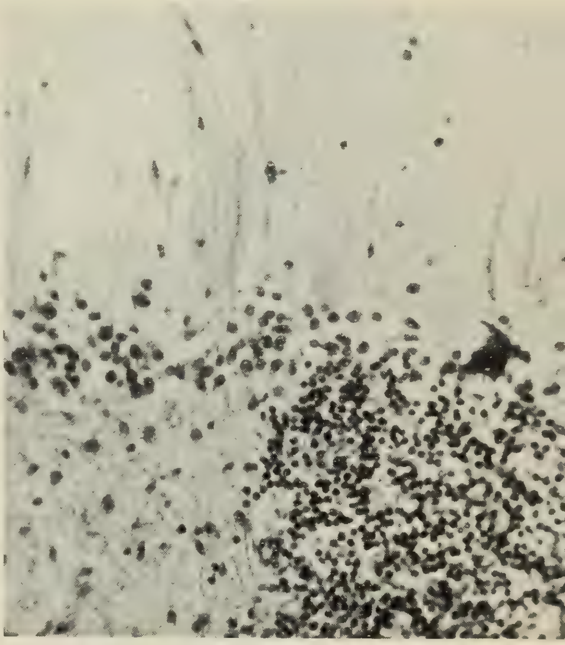

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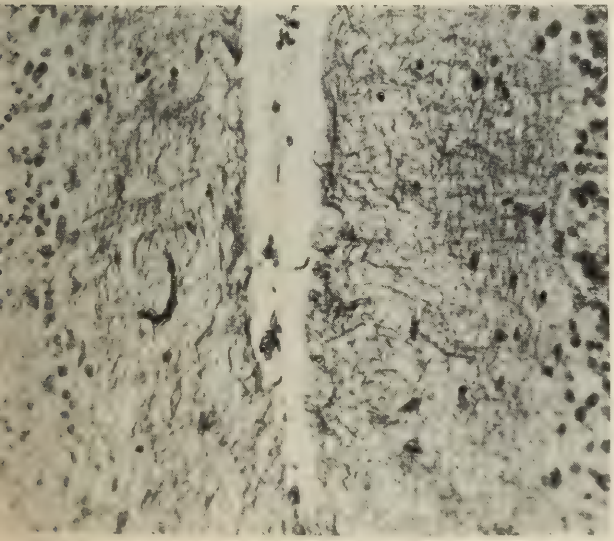

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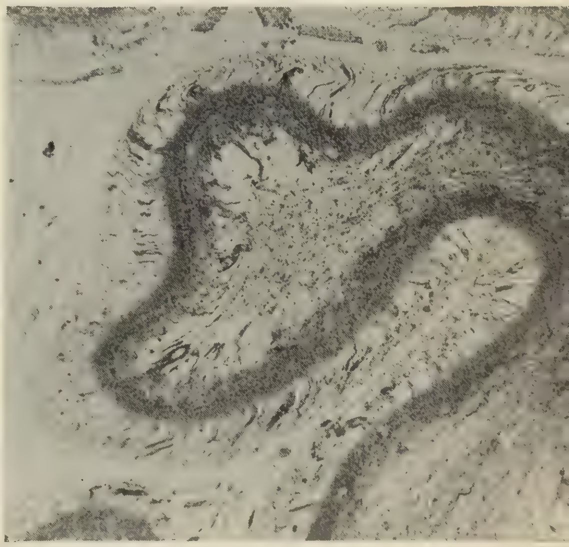

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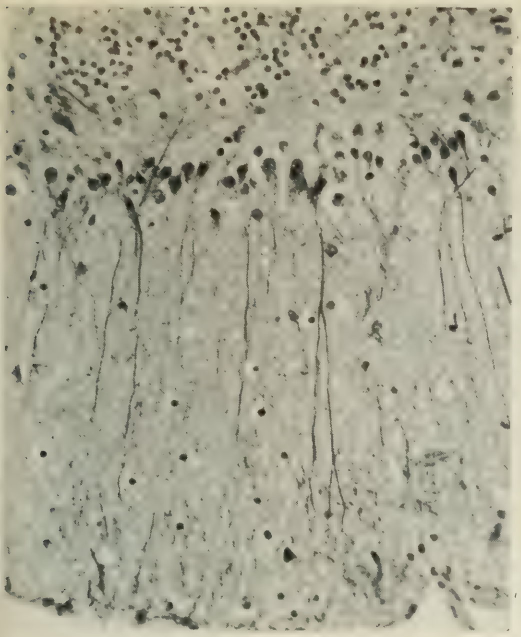

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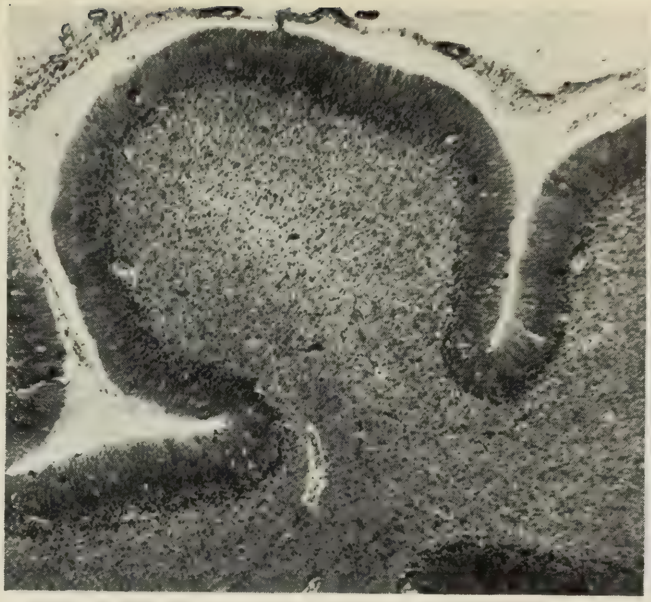

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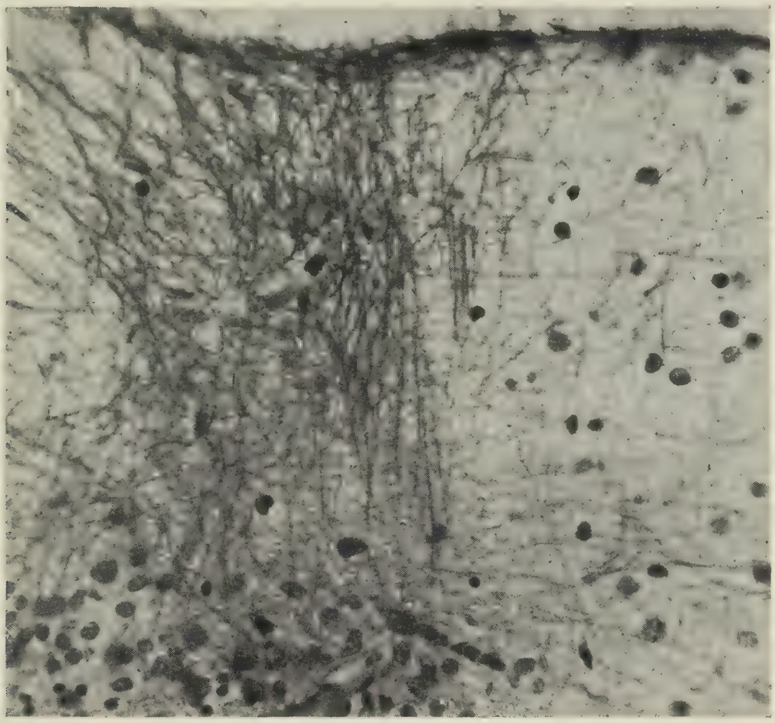

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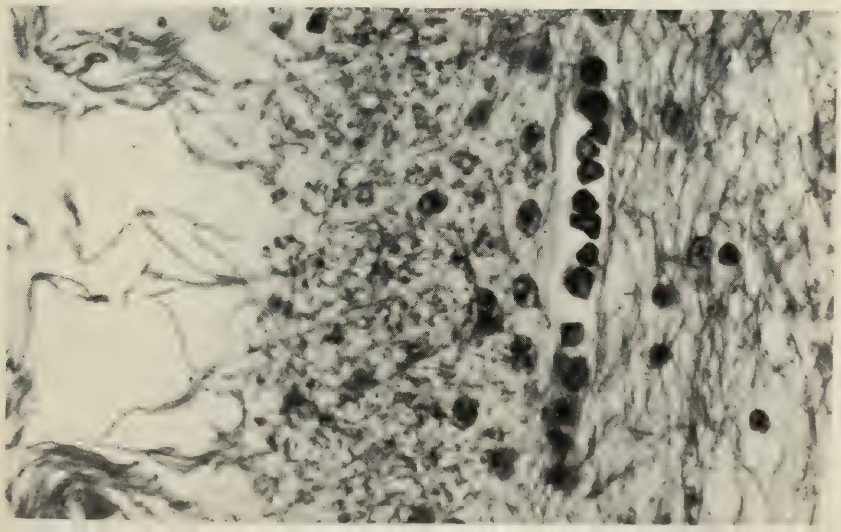

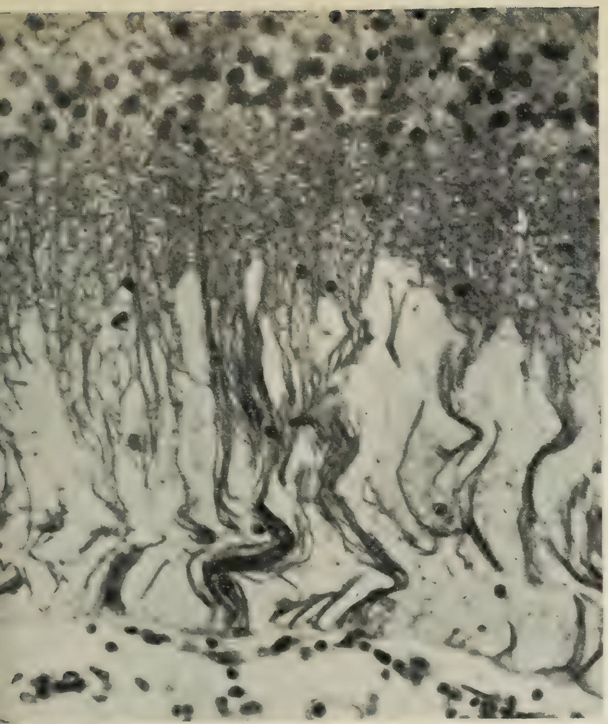

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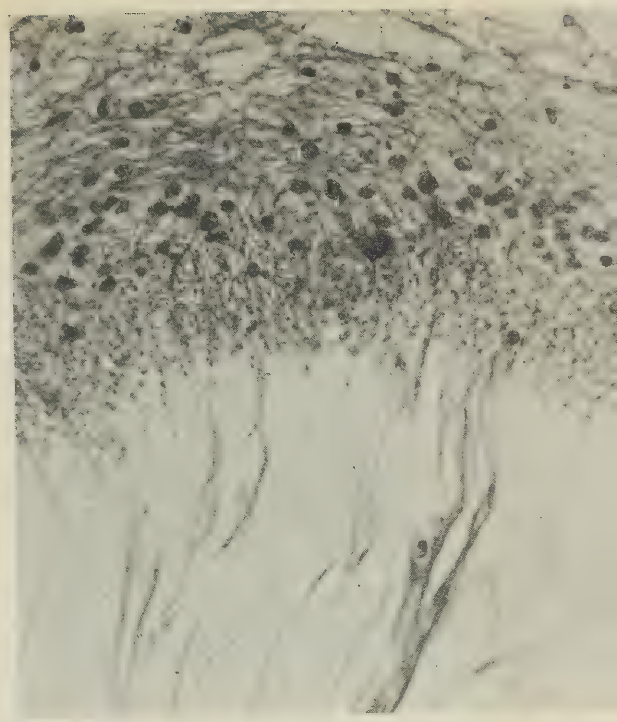

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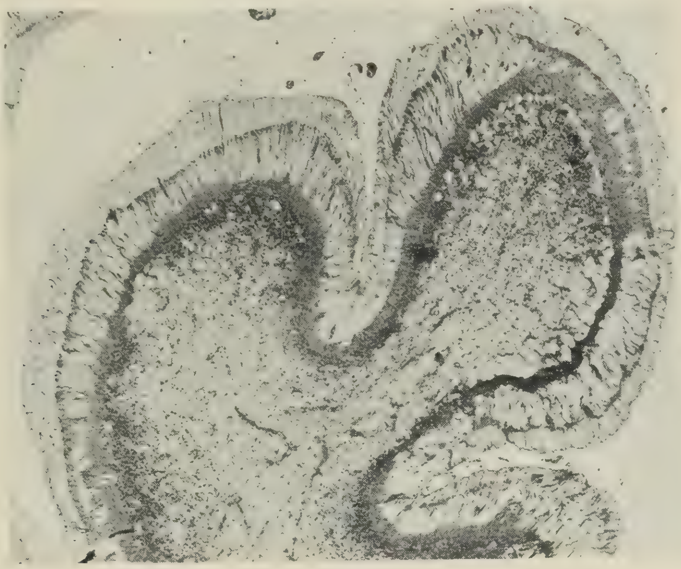

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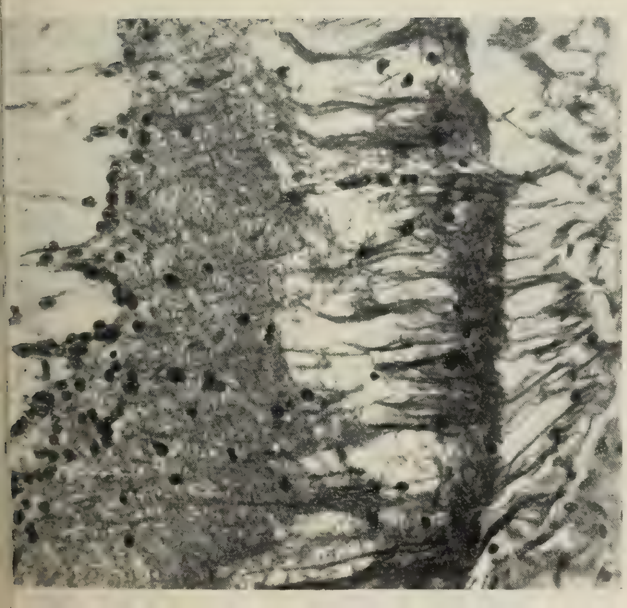

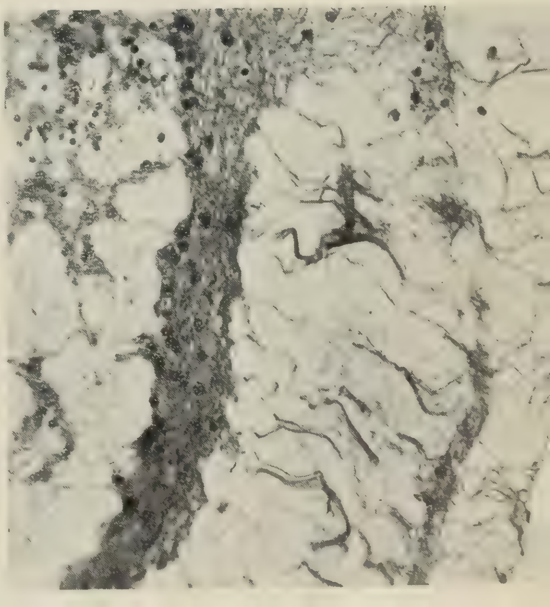

A Case of Cholesterin Stones in the Brain and Cord.

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BOSTON.

Reprinted from The Journal of the American Medical Association, December 2, 1905.

CHICAGO:
PRESS OF THE AMERICAN MEDICAL ASSOCIATION,
ONE HUNDRED AND THREE DEARBORN AVENUE,
1906.

A Case of Cholesterin Stones in the Brain and Cord.

A CASE OF CHOLESTERIN STONES IN THE BRAIN AND CORD.*

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BOSTON.

Following is a case of multiple cholesterin concretions found at autopsy in the brain and cord of a man who showed in life no signs referable thereto. About the masses there was a fibrillary overgrowth of neuroglia.

The patient was under clinical observation at the Boston City Hospital for a little over three weeks in the spring of 1904, on the medical service of Dr. C. F. Withington, whom I wish to thank for the use of his records. The patient was a man of 56, with extensive peripheral arteriosclerosis. For the most part he presented a plain history of cardiac disease growing worse: orthopnea, dyspnea, cyanosis, edema, all coming on in irregular spells, together with gradual enlargement of the heart area and feebleness of heart action, slight albuminuria, a fairly constant demonstration of a soft blowing systolic murmur at the apex transmitted to the axilla, and gradual development of dullness in lower backs. There were no signs directly referable to lesion of the nervous system. A frost-bite of the previous winter had failed to heal well in the right foot. He died a little unexpectedly during a slight apparent improvement in his cardiac symptoms.

The autopsy showed general and extensive arteriosclerosis. The coronary arteries were extensively yellowed and stiffened. The aorta showed diffuse sclerosis with calcification. The sclerosis of the circle of Willis was unusually extensive; and its primary and secondary

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* From the Pathological Laboratory of the Boston City Hospital.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

branches were involved. The heart showed considerable hypertrophy (weight, 615 grams) and diffuse yellowish thickenings of the mitral leaflets. The mitral orifice measured 11.5 cm.; the other valves were not abnormal. The heart muscle showed fine fat droplets in a very few fibers by the Scharlach R. method. Fresh extensive infarctions of the kidney were found, due either to thrombosis or to emboli, which had become in part organized. A hemorrhagic wedge-shaped area in the lower lobe of of the right lung was covered with fresh fibrin. The lungs in general were edematous and congested. The trunk showed little else abnormal save a fibrous pleurisy of the left side and chronic thickenings about the spleen and the liver. The organs of the trunk were examined and the liver. The organs of the trunk were examined by Dr. C. W. Duval, whom I wish to thank for his records.

The findings in the head were as follows:

Scalp, calvarium, dura normal. Sinuses contain fluid blood. Pia edematous, notably over vertex. Strips readily. Superficial veins contain no great amount of blood. Carotids yellow and stiff almost uniformly. Circle of Willis, with primary and sometimes secondary branches, focally yellow and stiff. Substance shows on external palpation no great variety of consistence. The brain is slightly moister posteriorly. The gyri are fairly firm. On section the substance of the anterior portions of the centrum semiovale in both hemispheres is of normal consistence. The posterior portions of the centrum semiovale are moister and softer than in front; brain substance clings to the knife on section. The edema and softening are more marked on the right hemisphere. At the junction of the gray and white matter of the posterior portion of the left middle temporo-sphenoidal convolution is a coherent, gritty, solid sliver of yellowish-gray material 1.5x1.0x0.3 cm., tightly adherent to the surrounding tissue. There is a similar spheroidal mass about 1 cm. in diameter, imbedded in the gray matter of the right inferior frontal convolution. Adjacent to this inferiorly about 1 cm. distant is a purplish-red, slightly translucent, smoothly cutting and slightly bulging area 1 cm. in diameter, in the inner zone of the cortex. Next this is a small indefinitely bounded area of moist, grumous, opaque, yellowish-gray material, possibly the product of occlusion of a medullary branch of the cortical arterial system; no embolus was found. No similar areas elsewhere. Ventricles contain more than a tablespoonful each of a clear fluid. Choroid plexuses slightly cystiform. Ependyma normal.

Basal ganglia normal and of the usual consistence, except in the middle of the left lenticular nucleus, which presents a stony mass 2 cm. in diameter and slightly flattened from before backward. The mass is closely invested by a thin fibrous capsule and does not shell out. On sawing the middle is found to contain soft opaque grayish material.

Isthmus, bulb and cerebellum normal. Cord: Pia edematous in the middle of the posterior columns of the lower cervical region are small, symmetrical gray areas, suggesting sclerosis. Gray matter everywhere retracts slightly from section surface. On the pia of lower dorsal cord is a single minute white calcified plaque.

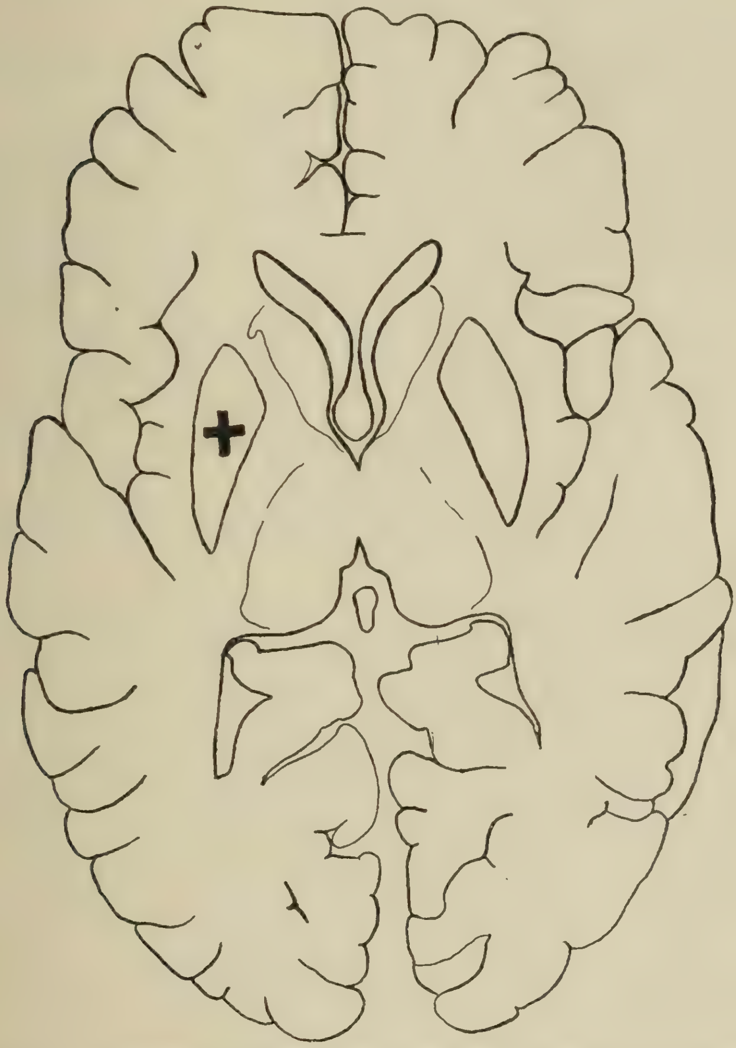

Fig. 1.—Diagram (Dalton, 1885, Series B, Plate vii) to show position of large cholesterin mass.

Microscopic examination of the organs of the trunk showed a slight brown atrophy of the heart muscle, a hemorrhagic infarct in the lung surrounded by a zone of cocci, chronic passive congestion of liver (extreme) and spleen, infarction of the kidney with zone of congestion and leucocyte invasion, an adrenal with high blood content, and a pancreas without notable lesion. There was evidence of arteriosclerosis throughout the organs.

Microscopic examination of the brain and cord showed a moderate subpial gliosis in several places examined. The cortex cerebri, except near the cholesterin masses, was not greatly altered. The tissue of the cord showed very numerous corpora amylacea.

The reaction about the cholesterin masses in the gray matter is slight. A teased specimen from the capsule about the mass in the lenticular nucleus was fixed in formalin and mordanted with picric acid, followed by ammonium bichromate and showed hairlike masses of neuroglia fibrils.

More notable is the reaction about the miliary masses in the white substance of the cord. These foci are grossly evident in sections of the cord fixed in Zenker's fluid, mounted in paraffin, and stained with phosphotungstic acid hematein. The cholesterin masses have become dissolved away; all that remains of a lesion is the cavity surrounded by a narrow zone in which nerve fibers and myelin sheaths are absent and replaced with a fine felt-work of neuroglia fibrils.

Flakes from various masses and from different portions of the large mass in the lenticular nucleus were found to consist chiefly of smaller and larger cholesterin crystals. No tubercle bacilli could be demonstrated among the crystals. One-half gram of material from the middle of the largest mass was injected into the groin of a guinea-pig, but tuberculosis did not follow.

It is not possible at present to give an adequate explanation of this finding. The condition has nothing in common with cholesteatoma, excepting cholesterin, and fails to show the essential element of cholesteatoma, viz., an accumulation of desquamated epidermal cells. It is not possible to prove a relationship of the deposits with the remains of tubercles, of gummata or of multiple abscesses. It is possible that the deposits are related with old lesions of the blood vessels, perhaps with occlusions or with changes in the vessel walls; at any rate, there is unusually widespread arteriosclerosis in the case. Whatever their origin, it is harder to account for their accumulation in solid tissues than in a cavity like the gall bladder.

The chief interest of the deposits must for the present remain in their association with multiple foci of sclerosis. Deposits like those in the cord may readily be overlooked in routine examinations, and the small spaces occupied by the crystals may be taken for artefacts in preparation. A more careful fresh inspection of central nerve tissues, and especially of the cord, may bring out more of such miliary or larger glioses, to which the attention was drawn in the present case only by the presence of large masses in the gray matter of the cerebrum. The case can hardly be unique. With more cases the relationship of the cholesterin with old foci of suppuration or with vascular lesions may be demonstrated.

SUMMARY.

Male of 56 years. General and extensive arteriosclerosis, extending to gross involvement of some secondary branches of the circle of Willis. Death from heart failure. Small masses of pure or almost pure cholesterin crystals in several parts of the cortical and central ganglionic gray matter and in the white matter of the spinal cord. Largest mass, 2 cm. in diameter, in middle of left lenticular nucleus. Thin capsules due to fibrillary overgrowth of neuroglia surround the masses. The relation of cholesterin to miliary glioses in the spinal cord may readily escape attention.

A CASE OF POTT'S DISEASE IN THE MONKEY

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(From the Pathological Laboratory of the Boston City Hospital)

Reprinted from
The Journal of Medical Research, Volume XIV., No. 2
(New Series, Vol. IX., No. 2), pp. 393-398, January, 1906

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A CASE OF POTT'S DISEASE IN THE MONKEY.*

E. E. SOUTHARD, M.D.

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(*From the Pathological Laboratory of the Boston City Hospital.*)

Following is a case of tuberculous caries of the lumbar vertebræ in a monkey (*Macacus cynomologus*). The tissue changes in the spinal canal were demonstrated by means of several stains, in particular by Mallory's phosphotungstic acid hematein method after Zenker's fixation.

I. HISTORY.

The monkey, a half grown male *Macacus cynomologus*, was brought to the Biological Laboratory to be killed on account of paralysis of the hind limbs. The animal, which had been kept for some months as a pet in an American family, had shown loss of power in the hind limbs for several weeks.

On examination at the laboratory he was found tame, friendly, and in good spirits. Only ten centimeters of the tail remained, and the tip of the stump was the site of a small chronic ulcer.

The monkey dragged himself about by the forelegs, sometimes laid down, but as a rule assumed a semirecumbent posture with hips rotated forty-five degrees to the left, and hind legs flexed but flaccid. With the left forepaw placed on the lumbar region, position was retained by balancing on the right forepaw.

There was no facial expression denoting pain. The animal did not cry out. No pain reaction was evoked by pressure on the spine. Sensation was absent below the belt line; there was, however, frequent picking at the tail ulcer.

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* Received for publication Dec. 1, 1905.

NOTE. — I am indebted to Dr. W. E. Musgrave of the Government Biological Laboratory in Manila for the monkey and for permission to report the findings, and to my colleague, Dr. W. R. Brinckerhoff, for the autopsy protocol and microscopic work on the organs of the trunk.

II. AUTOPSY.

The monkey was chloroformed and autopsied at once (W. R. B.).

Well developed and nourished. Skin normal except at stump of tail. Viscera of trunk normal except spleen, which shows numerous round, opaque, gray areas two millimeters or larger in diameter. All lymph nodes normal.

Brain shows no lesion.

Spine. — Cord exposed by sawing through the transverse processes of the vertebræ. Outside the dura in the lumbar region on the left side is a pale gray-yellow gelatinous mass, composed of small semitranslucent nodules (about two millimeters in diameter) irregularly fused together and imbedded in a matrix of similar, more opaque material. The gelatinous mass is adherent both to the dura and to the wall of the spinal canal. The anterior and lateral aspects of the canal opposite the first, second, and third lumbar vertebræ are affected for a distance of five and five-tenths centimeters. The material is deepest and widest opposite the second lumbar vertebra, where it spreads over one-third of the circumference of the canal. The cord was removed with the dura mater intact. Sagittal sections of the spinal column show opaque yellow areas in the bodies of the first, second, and third lumbar vertebræ; the areas are most extensive in the second. The dorsal portions of the vertebræ show softened, more opaque foci. The yellow areas of the second, lower posterior portion of the first, and upper posterior portion of the third lumbar vertebræ are continuous with the mass in the canal. The disks between the affected vertebræ are involved posteriorly. The other disks and vertebræ are normal.

III. MICROSCOPIC FINDINGS.

Sections of the lung, liver, kidney, intestine, testicle, epididymis, and lymph nodes show no lesion. Spleen shows areas in the pulp which are in part replaced with epithelioid, connective tissue, and giant cells, in part necrotic and infiltrated with polynuclear leucocytes. Section of the tail stump shows chronic inflammation.

For the microscopic examination of the cord and membranes, the following methods were used: eosin and methylene blue, phosphotungstic acid hematein, anilin blue connective tissue stain, Weigert's myelin sheath stain, and Marchi's method for fat.

At the level of the severest lesion, opposite the second lumbar vertebra, the dura mater has been pierced by the process, and an ovoid mass, .3 x .2 centimeters, of tubercles containing giant cells abuts upon the subarachnoid space. At this level the cord and the nerve roots are together displaced backward to the posterior portion of the dura, which is itself closely applied to the wall of the spinal canal.

The dura is elsewhere preserved. Its inner layers are denser than usual opposite the tubercles and infiltrated immediately about the tubercles with great numbers of cells of the lymphocyte and plasma cell series. At the points of greatest pressure, as opposite the extradural tubercles and posteriorly at the level where the whole cord is compressed by the subarachnoid mass, the dura exhibits strata on its inner surface, two to four cells deep, composed of cells with oval vesicular nuclei and tapering cell bodies. Between these run a small number of connective tissue fibrils. Collections of similar cells with a few connective tissue fibrils are found free at several points in the subarachnoid space and are probably to be regarded as cross-sections of compressed subarachnoid trabeculæ.

The nerve bundles of the cauda equina are nowhere submitted to extreme pressure except at the one point of subarachnoid invasion. Here an occasional ventral root bundle exhibits a diffuse increase in the interstitial cells and an unusual prominence of the minute vessels with swelling and occasional evidence of division in the lining cells. This vessel change either antedates or has little relation with the interstitial change, since such vessel changes are frequently seen, and seen also in otherwise normal root bundles. It is more likely that the increase in interstitial cells is related to a change in the myelin, since adjacent sections of the same bundles, stained with Mallory's connective tissue stain, show a loss of the red-staining myelin and the fiber spaces filled with a faintly blue-staining homogeneous substance. The Marchi preparations also favor the explanation of the interstitial changes as a reaction to myelin change. Precisely the same bundles cannot be followed, however, and the interstitial changes are harder to interpret in Marchi preparations.

The pia mater has no share in the lesion. There are no variations in depth of the layer to correspond with the surrounding lesions.

The lesions of the cord are of interest. Sections of various levels, stained for fatty degeneration by the Marchi method, show blackening of a scattered but almost symmetrical character, which in the higher levels becomes confined to the outer fourth of the posterior columns and narrow strips at the lateral borders of the lateral columns. Sections of adjacent segments, stained for myelin by the Weigert method, show no change. On the contrary, adjacent segments, stained by the phosphotungstic acid hematein neuroglia method (Mallory), show increase of neuroglia fibrils in the same areas which are blackened by the Marchi method. These new fibrils are still found in close spatial relation with neuroglia cell bodies. Recourse to the eosin and methylene blue method of staining shows that the neuroglia cells, responsible for the fibrillary gliosis, have large cell bodies and large vesicular nuclei with prominent nucleoli. Active neuroglia changes with new fibril formation are therefore demonstrable in this case in the fatty stage of secondary degeneration.

The neuroglia fibril content of the spinal cord of the monkey can be well demonstrated by the phosphotungstic acid hematein method. The higher levels in this case stain better than the edematous levels opposite the tuberculous masses in the lumbar region. In the upper levels the fibril content of the subpial region and of the white matter approximates the fibril content of the same region of the human cord after similar fixation. The fibril content of the gray matter in the monkey's cord is also high, but the neuroglia about the central canal is much less dense than that in adult man.

The nerve elements of the cord in this case show little beyond the effects of secondary degeneration. As mentioned in the account of the root bundles, the anilin blue connective tissue stain is useful, employed in sections adjacent to sections stained with eosin and methylene blue, and with phosphotungstic acid hematein. The loss of myelin, which normally stains yellowish red, as a rule in the form of a delicate reticulum, is readily made out with the anilin blue stain.

Spaces in the white matter, similar to the spaces familiar in the human cord in pernicious anemia and like conditions, are seen also in this cord. They are most frequent in the posterior and anterior columns in the levels opposite the tuberculous masses. The spaces, which are sometimes fifty to one hundred microns in diameter, are often filled with homogeneous material or granular coagulum, and occasionally contain a mononuclear cell, possibly an endothelial cell.

The nerve cells of the cord fail to show important changes. A few only show the axonal reaction. In almost all the nerve cells the Nissl granules stain well; but, in the levels opposite the severest lesion, some of the cells are reduced in size, apparently from loss of substance between the granules.

IV. SUMMARY.

1. A half grown pet macacus, autopsied several weeks after onset of paraplegia, showed tuberculosis of the spleen and of the lumbar spine. There were extra dural masses opposite the upper three lumbar vertebræ together with penetration of the dura and compression of the cord at the second lumbar vertebra.

2. The neuroglia fibrils in Macacus cynomologus can be demonstrated well by the use of the phosphotungstic acid hematein method after fixation in Zenker's fluid. The picture approximates that of the human cord similarly treated. The extent and character of the neuroglia changes

found in this case suggest profitable lines of experimental work on cellular and fibrillary gliosis in the monkey.

3. Areas of secondary degeneration in this case, studied comparatively by the methods of Marchi for fat, of Weigert for myelin, and of Mallory for neuroglia and for connective tissue, demonstrate active neuroglia changes with new fibril formation in an early stage of secondary degeneration. The fatty degeneration is attended with fibrillary gliosis, the onset of which antedates a demonstrable loss of myelin.

4. The connective tissue cells in degenerated nerve bundles in the cauda equina show activity analogous to the neuroglia cell changes found in the cord.

The Journal of Medical Research, Vol. XIV., No. 2, January, 1906.

CYSTIC APLASIA OF THE CEREBRAL HEMISPHERES IN AN IDIOT CHILD

W. N. BULLARD, M.D.
AND
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(From the Pathological Laboratory of the Boston City Hospital)

Reprinted from
THE JOURNAL OF MEDICAL RESEARCH, VOLUME XIV., No. 2
(New Series, Vol. IX., No. 2), pp. 431-438, January, 1906

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CYSTIC APLASIA OF THE CEREBRAL HEMISPHERES IN AN IDIOT CHILD.[*]

W. N. Bullard, M.D., and E. E. Southard, M.D.

(*From the Pathological Laboratory of the Boston City Hospital.*)

The case we here present was one of idiocy in a child which showed an unusual condition of cystic aplasia in the cerebral hemispheres. Some points in the histopathology of the cerebrum, together with developmental modifications in some organs of the trunk, serve to point out a field of work in idiocy

CLINICAL SUMMARY.[†]

Defective girl, born without the use of instruments in the eighth month, one of twins (the other still-born). Slight evidence of consciousness or orientation. General rigidity. Food given with difficulty. Constipation. Convulsive seizures began after twentieth month. Death in thirty-seventh month.

Gross findings. — The autopsy was performed February 4, 1904 (E. E. S.). A description of the findings in the head, together with a summary of trunk findings, follows:

Head. — Profuse growth of curly, fair hair. Scalp normal. Cranium somewhat abnormal in shape. The occipital bone bulges from the plane of the parietals, as if posterior fossa were relatively larger than the other fossæ. The left posterior quadrant of the vault bulges smoothly from the general surface. There is no evident flattening of cranium in opposite quadrant. Bones can be separated along suture lines with no great violence. Dura tightly adherent to calvarium.

Brain hardened in toto in formalin. Gelatine was injected beneath pia mater of the hemispheres. The cortical wall is thinnest in the posterior halves, and an artificial bulging was produced in the occipital and posterior parietal areas.

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[*] Received for publication Nov. 5, 1905.

[†] The full clinical history is given in Med. Surg. Reports of Boston City Hospital, 1905, Article X.

Externally the hemispheres are roughly normal and symmetrical in shape, but fail to show the usual furrows when viewed from above. The brain is almost smooth at both poles when viewed from above, but a tongue of solid tissue with sulcal markings runs from below upwards and backwards in the locus of the central convolutions. From below, the hemispheres are, in general, of a normal appearance. On section the greater portion of the cortex is found to be replaced by wide cystic spaces, freely intercommunicating and traversed by slender lace-like smooth trabeculæ, a few millimeters in diameter. The system of ventricles is independent of the cortical and central cavitation; but the roof of the lateral ventricles is only a few millimeters thick. None of the ventricles is notably dilated.

The cerebellum shows no reduction in size and has the usual markings.

ANATOMICAL DIAGNOSES.

Extensive cystic spaces in upper portion of cerebral hemispheres, best marked near both poles.

Cranial changes, corresponding to cerebral maldevelopment.

Backward muscular development.

Supernumerary spleens.

Malnutrition.

Broncho-pneumonia of right lower lobe.

MICROSCOPIC FINDINGS. — The microscopic work was carried out with a view of getting evidence on the cause and conditions of the maldevelopment. Result was taken to general stains (eosin and methylene blue, the anilin blue stain for connective tissue, and the phosphotungstic acid hematein stain*).

The *organs of the trunk* showed a few points of interest. The immediate cause of death was probably broncho-pneumonia, since foci in the *lung*, 0.5 centimeter or more in diameter, contain an exudate made up almost purely of leucocytes, and there is edema and cell infiltration of many air spaces elsewhere. The bronchial mucosa is as a rule preserved. Near a few bronchi there is a limited amount of lymphoid tissue containing eosinophiles and mast cells. Near the root of the lung there are better defined lymphoid nodules adjacent to plates of cartilage; most of the cells therein have vesicular nuclei and very little cytoplasm, but a few of the cells have nuclei with chromatin murally arranged.

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* F. B. Mallory. A Contribution to the Classification of Tumors. Journ. Med. Research, xiii, 2, January, 1905.

The tissues of the neck were explored for *thymus* tissue, which was found in limited amount and in a few blocks only. The thymus tissue occurs in acini, which are as a rule not over one millimeter in diameter but are now and then drawn out into slender masses 0.5 centimeter long. The acini are surrounded by dense fibrous tissue without cell infiltration. The acini themselves show extensive fibrous change and in places an undue proportion of small vessels. The thymus lymphocytes are few in number by comparison with the larger cells of the connective tissue series. Only a few acini contain thymus pearls. The total amount of thymus tissue found could be contained in an area one centimeter in diameter. The character of the tissue suggests advanced atrophy rather than backward development.

Of the other ductless glands, the *thyroid* was well developed, and showed its secretion largely within the gland spaces. The parathyroids were not found, but no extensive search was made for them. In the *hypophysis* small canals lined with low epithelium were found between the glandular and nervous portions. A few gland spaces contain small plugs of colloid material. The number of eosinophile gland cells is low.

The *spleen* and accessory spleens showed, besides central lesions of the Malpighian bodies probably related to the terminal infection, some peculiarities in the pulp tissue. The most striking feature is the presence of numerous nucleated red blood cells (one or more to an oil immersion field) as a rule of normal size, but often larger than normal. These cells are found both in blood vessels and in the sinuses. The majority of cells in the spleen are a series of cells of various size with vesicular nuclei; these cells are probably derived from endothelial cells lining the pulp spaces. Cells approximating the adult lymphocyte type occur, but are scarcely more frequent than the nucleated red blood cells. The cells of the Malpighian bodies have nuclei rather larger than lymphocyte nuclei, as a rule of a frankly vesicular character, but in some cases assuming a peripheral arrangement of chromatin. These and other features make the spleen difficult of interpretation; there is no evidence of a destructive process for red cells or other cells.

The *heart* showed no lesion except vacuolation of a few fibers.

The *liver* appears normal. The portal veins and the sinusoids of the lobule centers are congested. The liver cells frequently contain numerous small brown or greenish brown granules. The periportal connective tissue is thin but dense, and shows now and then a mast cell.

The *pancreas* and *adrenal* are not remarkable.

The *kidney* shows a degree of development corresponding with that of a child of a year or under.

Brain. — The pia mater is everywhere thin and without lesion. Some of the deep processes which accompany vessels into the interior are considerably broader than is appropriate for the caliber of the vessels. These expanded perivascular spaces contain fluid and many phagocytic cells. The spaces are lined by smooth, abrupt walls of compact neuroglia.

It is often possible to follow along the pial processes till they open out upon the broad cystic spaces which make up a large proportion of the cerebrum. There is no free passage into the interior; both hemispheres held injection perfectly.

The larger cystic spaces are lined by a thin layer of fairly dense fibrous tissue. This fibrous lining becomes expanded in the narrower recesses to contain phagocytic cells. The features of a cyst of softening may be roughly reproduced in a few places. The anilin blue connective tissue stain at once corrects this impression by demonstrating a sudden transition between the compact wall of neuroglia tissue (staining red) and the fibrous wall (staining blue).

The characters of the cyst lining scarcely differentiate it at first glance from the pia mater. The pia mater, however, contains large vessels, and the cyst lining is supplied, as a rule, with capillaries only. Moreover, the pia mater is backed by a cellular neuroglia readily distinguished from the compact neuroglia behind the cyst lining.

Besides the cystic spaces lined with fibrous tissue there is another kind of cyst, small, lined with ependyma, and associated with, or opening into, the ventricles. These cysts were found chiefly adjacent to the posterior cornu, in a site where they occur, as is well known, not infrequently in apparently normal adults. There is no sign that these accessory ependymal cysts dilate extensively, if at all.

The ependymal cysts and the ventricles show cells supplied with long, hair-like processes, which seem to be attached in many cases to basal bodies near the outer surfaces of the cells.

There are occasional gaps in the ependyma lining the ventricle, and adjacent to these the neuroglia cells may be heaped up in small masses. Corresponding with the smaller gaps in the ependyma, the dense subependymal band of neuroglia is demonstrably interrupted and replaced by a looser tissue, in which the more active neuroglia cells, with expanded cell bodies, are found. In some cases the ependymal rupture demonstrably involves the subependymal tissues as well as the line of ependymal cells.

The architecture of the cortical remains is far less familiar in appearance than that of the ventricular region. The narrow strips of tissue which represent considerable stretches of cortex present a regular stratification, such that the peripheral portion is almost constantly more cellular than the underlying or fibrillar stratum. The appearances suggest that the cellular layer corresponds with the cortical gray matter, and the fibrillar layer with the central white tissue or its neuroglia framework.

There is in many places a thin stratum representative of the subpial layer, in which a few fibrils run parallel with the pia. Among these fibrils are a few vesicular nuclei with prominent nucleoli. These nuclei vary in size, but average the diameter of the blood globule with the same fixation. On approaching the larger pial processes the subpial layer of neuroglia gradually thickens, becomes more cellular, and begins to show occasional stouter fibrils. As the layer dips inward along the pial process, it becomes gradually transformed into a less cellular and more fibrillar and compact neuroglia tissue lining the cysts.

There are several variations in the structure of the tissue which represents the cortex. In a given area the structure is fairly regular. The most frequent variation is the appearance of stout bundles of fibers, at regular intervals in the loose intermediary layer of the cortex, running perpendicular to the pia mater. In other places the nuclei accumulate in small foci at regular intervals so that the arrangement of nerve cells in some parts of the normal cortex is imitated.

There is little evidence of gliosis, either cellular or fibrillar, in the sense of the reactive gliosis of adult tissue. In places there is a more dense and compact arrangement of fibrillar masses underneath the cyst lining; if this is reactive gliosis, it is without doubt not recent.

The *cerebellum* shows a normal stratification, numerous Purkinje cells, a molecular layer filled with cell processes, and a granular layer in places thin, but as a rule normal. The vessels, particularly in the dentate nucleus, are dilated. Neuroglia tissue is nowhere prominent; there are occasionally a few coarse fibrils along vessels.

The *medulla* shows a well-developed olive and accessory olives in the levels examined. The pyramidal tracts are lacking, or represented by few fibers. There is no gliosis of the ventral regions. There is very little hint of gliosis elsewhere, except along the upper lateral border.

GENERAL SUMMARY AND REMARKS.

1. An infant, born in the eighth month of pregnancy, one of twins (the other still-born), was backward in development,

gave evidence of extensive nervous defect, with numerous convulsive seizures, and died, when thirty-seven months old, of broncho-pneumonia.

2. The autopsy showed gross cerebral changes. The ground plan of the cerebrum was preserved, but the substance of each hemisphere was largely replaced by a closed cystic cavity, independent of the ventricles. The interiors of the cystic cavities were traversed by delicate strands of neuroglia tissue. The pyramidal tracts failed to develop. The cerebellum had developed almost normally.

3. The nature and time of the original injury cannot be exactly fixed. The agent was probably focal and just severe enough to destroy the nerve cells or nerve cell producing cells, but leave the neuroglia cell-series intact and capable ultimately of producing fibrils. The effect of this differential aplasia is that neuroglia tissue alone serves to maintain much of the ground plan of the cerebral cortex.

4. Although the original injury may have been quite limited in extent, the failure of cell-processes and whole fiber systems to develop coördinately with the expansion of the cerebrum, has increased the ultimate loss of solid tissue many fold.

5. It is probable that the cystic chambers in the cerebrum are in part due to the dilatation of perivascular spaces, with eventual rending apart of their walls, as the brain plan continues to enlarge, and the neuroglia masses contract. There are phagocytic cells in recesses along the fibrous walls of the cystic spaces. It is not clear whether the neuroglia tissue or one of the brain envelopes is the leading tissue in the enlargement of the brain plan.

6. The case showed very little thymus tissue, which was largely overgrown by cells of the connective tissue series. The kidneys were backward in development. There were some peculiarities of the spleen. It is not yet possible to say what part is played herein by the cerebral defect.

DESCRIPTION OF PLATES.

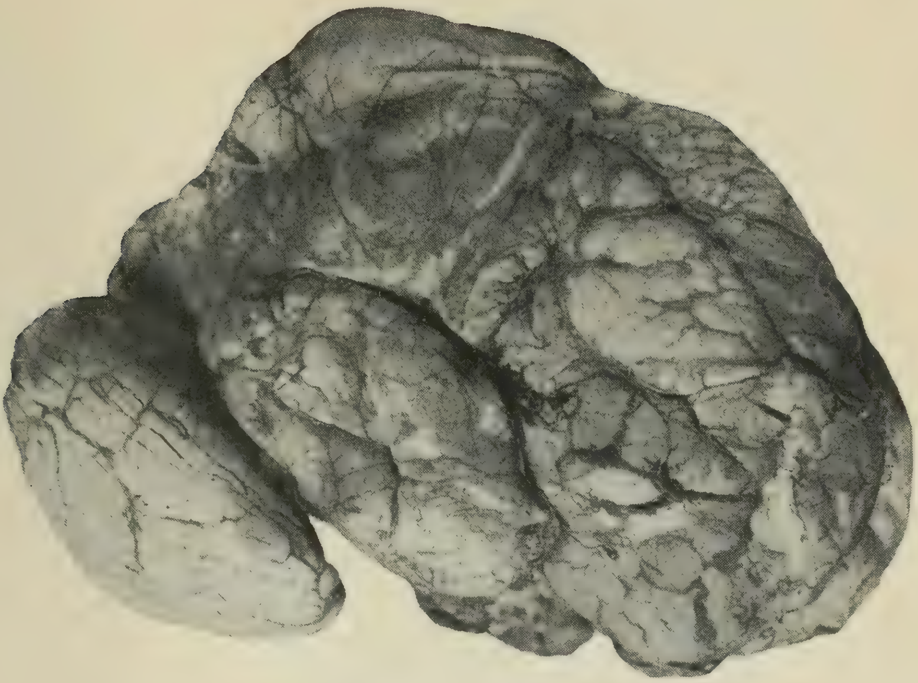
Plates XII., XIII., XIV. Photographs of brain after injection of the cavities in the substance of each hemisphere with formalized gelatin. The irregular bulging of the posterior part of each hemisphere is in part artificial.

Plate XII., Fig. 1, right side; Fig. 2, left side.

Plate XIII., Fig. 3, view from above.

Plate XIII., Fig. 4, and Plate XIV., Figs. 5 and 6. Cross sections showing closed system of ventricles and cystic spaces in substance of hemispheres, with delicate trabeculation. The trabeculæ were found microscopically to consist of columns of neuroglia tissue invested externally with fibrous tissue; the walls of the cystic cavities showed in a few places phagocytic cells.

The Journal of Medical Research, Vol. XIV., No. 2, January, 1906.



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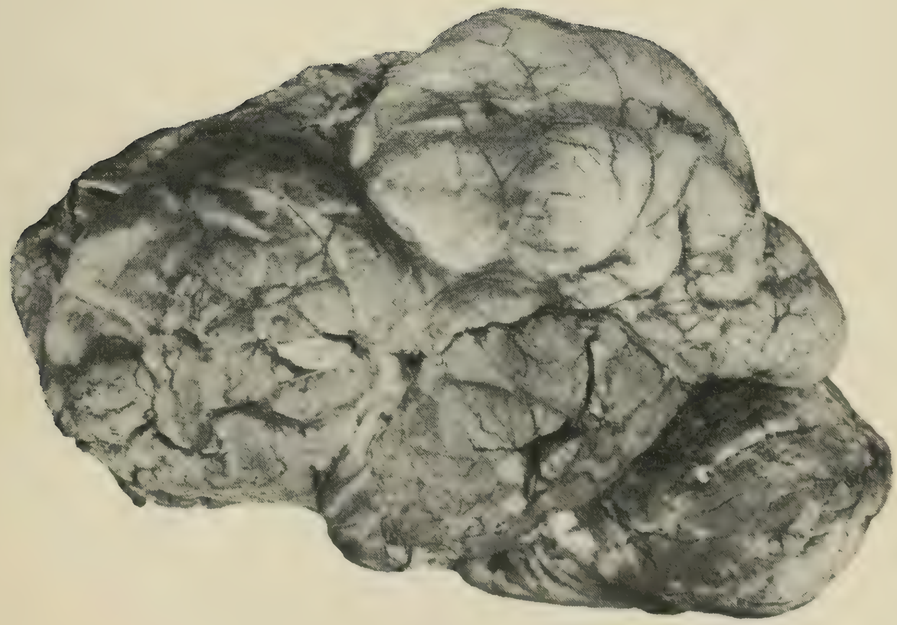

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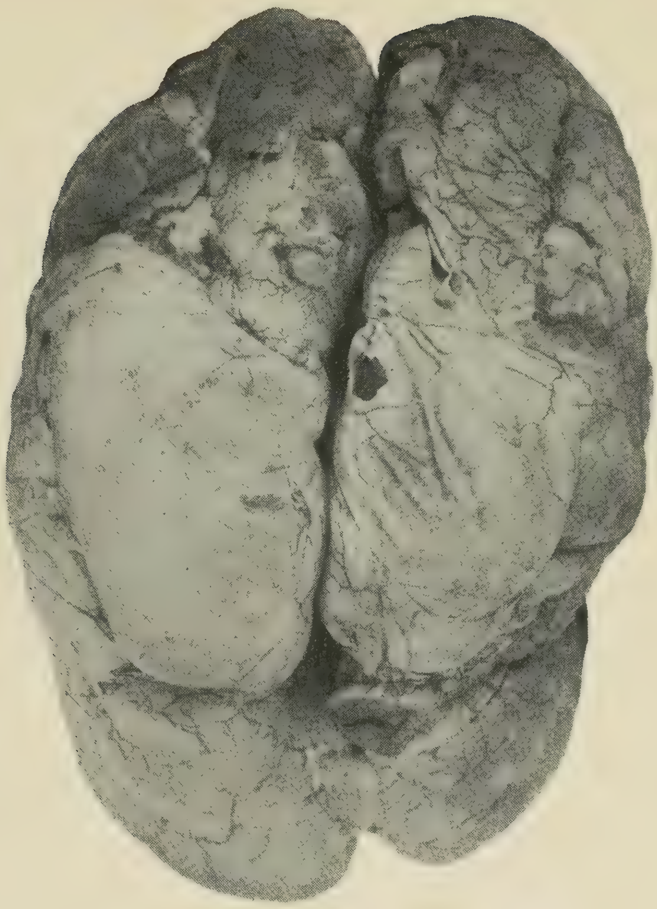

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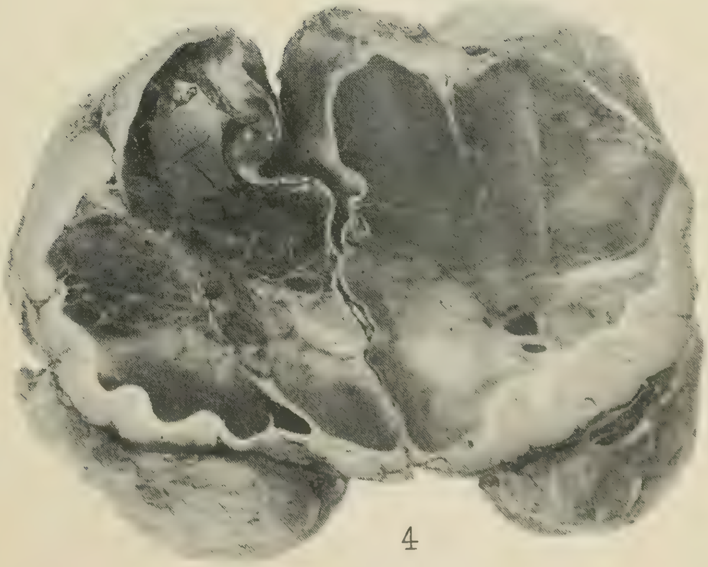

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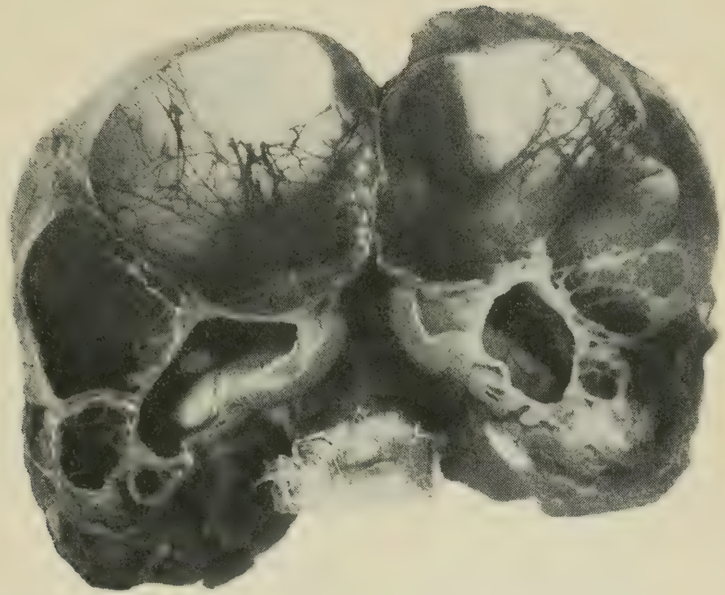

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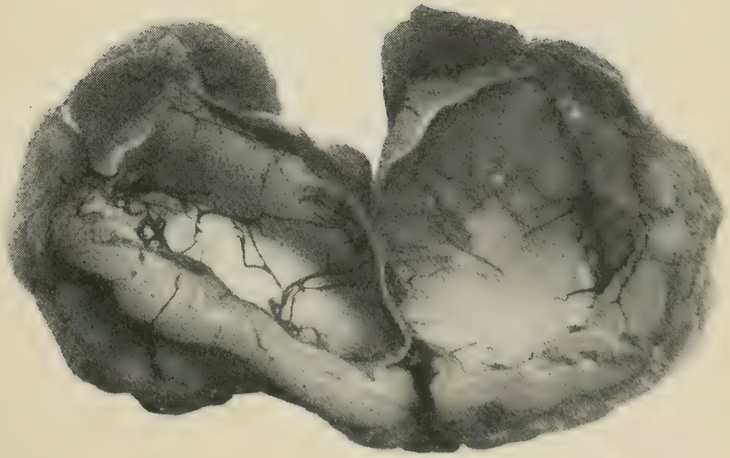

6

Diffuse Gliosis of the Cerebral White Matter in a Child.

By W. N. BULLARD, M.D.
and
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Reprint from THE JOURNAL OF NERVOUS & MENTAL DISEASE, JANUARY, 1906.

DIFFUSE GLIOSIS OF THE CEREBRAL WHITE MATTER IN A CHILD.

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The case here reported was that of a child which, after a fall on the back of the head, gradually lost power to walk, grew deaf, dumb, blind, and stupid, and died twelve months after the fall. The autopsy showed a peculiar overgrowth of neuroglia, with some destructive properties, confined to the white matter of the posterior parts of the cerebrum, optic thalami, and areas in the white matter of the cerebellum.

I. CLINICAL HISTORY.

Dr. Bullard.

Edward J., six years old, born in Boston, was first seen January 16. 1904.

There was no history of inheritance. Parents were healthy. There were ten children, patient being the eighth. Of these five were dead, four of "stomach trouble" and one of "meningitis."

The patient had always been well up to the time of the present trouble, except for measles when three years old.

Present trouble: Six months ago while playing in the cellar he fell backward down three steps. He was not unconscious, but got up himself and came up stairs crying. He seems to have had some nose-bleed, and possibly bleeding from one ear. The night following he was feverish and restless, but not apparently delirious. The next day he seemed well, and went out to play as usual. He did, however, have nose-bleed whenever his face was washed.

Since the accident he has been "nervous," and for five months he has had some difficulty in walking, staggering so that he is obliged to put out his hands to steady himself. Has never fallen from this cause. Can use his knife and fork. Mother thinks he is becoming stupid. Frequency of micturition. Is very deaf and has been taken to the Eye and Ear Infirmary, where operation for adenoids was advised.

Physical examination: Same as before, but now he obeys no directions and does not appear to understand or notice what is going on about him. Cries when examined. Walks with very short steps swaying from side to side.

Dr. Holmes (Aural Department) reports: No aural signs to account for the deafness, which is apparently of nerve origin.

July 6. Dr. Williams (Eye Department) reports: Some atrophy of each optic nerve, but not enough to account for almost total lack of vision. The latter is presumably of cerebral origin.

July 13. Was admitted to the Hospital Second Surgical Service, Dr. Monks. Temperature normal. Pulse 100-120.

July 18. Operation. Dr. Monks. Trephined about 1½ inch behind and 1 inch above right ear. Dura thickened. No visible cerebral pulsation. Dura opened. Pia slightly thickened, edematous. Several drachms of clear amber-colored fluid drawn from lateral ventricle.

July 20. Died.

II. ANATOMICAL FINDINGS.

Permission was granted to open the cranial cavity. The examination was made fifteen hours after death by Dr. R. L. Thompson, whom we wish to thank for his record. The child was 129 cm. long. Development fair. Nutrition good. Pupils equal, 5 mm. wide. Circumference of skull 53 cm. Frontal suture well marked. Surgical opening 1 cm. square in squamous portion of right temporal bone, 5 cm. above and behind external auditory meatus. Dura everywhere adherent to calvarium.

Brain with pia mater weighs 1,445 gms. Pia mater and vessels normal. Convolutions symmetrical. Substance very firm toward occiput. Ventricles contain a normal amount of fluid tinged with blood. Cruor clot, 2 cm. in diameter, in descending horn of right ventricle.

The white matter of the posterior part of the centrum semiovale in both hemispheres is replaced with grayish or straw-colored slightly translucent material of a dense consistence. The lesion is somewhat sharply limited to the white matter; the cortex, of a paler color, sinks below the surface of section. In the right occipital region there is a narrow layer of less dense white matter between cortex and lesion.

The areas of increased density were roughly marked out at autopsy. On the right the lesion involves and in part replaces the white matter of the occipital, parietal, and temporal lobes. The right optic thalamus is somewhat firmer than normal. In the left hemisphere the lesion is still more marked and almost everywhere replaces the white matter of the occipital, parietal and temporal lobes. The left optic thalamus is even firmer than the right. The lesion on the left side stretches at least 1 cm. anterior to a frontal plane taken just in front of optic thalamus. Pieces were removed for fixation in Zenker's fluid, and the rest of the brain was hardened in 10 per cent. formaldehyde.

III. MICROSCOPIC FINDINGS.

The sclerosis of the cerebral substance preserves on microscopic examination the same remarkable limitation to the central white matter which was noted in the gross. Except in the optic thalami, the limits of the white matter are nowhere transgressed by the neuroglia overgrowth. The exterior of the lesion in some parts of the occipital region follows the contour, and coincides precisely with the inner limits of gray matter. But, in general, the sclerosis corresponds rather to the body of white matter known as the centrum semiovale and may spare the intragyral portion of the white matter.

In spite of the massive character of the lesion, and the compactness of many portions of its structure, the overlying cortex fails to show major lesions, such as secondary changes in nerve cells due to the loss of their processes, or accumulations of phagocytic cells in vessel sheaths, or a reaction on the part of the neuroglia. It is noteworthy that even the upper or subpial layer fails to show a reaction on the part of the neuroglia, despite the frequency of this reaction under numerous conditions. The pia mater and its vessels are likewise free from lesion.

The extent and nature of the damage done by the lesion cannot be exactly determined. The volume of brain tissue remains unaltered or has been slightly increased by the lesion. There has been at some time considerable destruction or alteration of tissue in the region, as is shown by dense deep masses of pigment-bearing phagocytic cells in the sheaths of the appertaining vessels. The myelin sheaths, and doubtless numerous axis cylinders, have been destroyed in the area of sclerosis. In certain areas which seem paved with neuroglia giant cells separted by a few delicate neuroglia fibrils, it is certain that the original elements must have been destroyed.

In other parts it is by no means certain that all or even the majority of the axis cylinders have been dissolved in the lesion. In a preparation stained with phosphotungstic acid hematein (Mallory) it is possible to follow certain myelinated fibers, in whose myelin sheaths a delicate skeletal substance may stain, till the fibers enter the sclerotic area and lose their myelin. Neither myelin nor the delicate substance within the sheath can be demonstrated in quantity within the sclerotic area.

The anilin blue stain (Mallory) for connective tissue is of service on this point. It is possible for instance, to demonstrate in this case, by means of the anilin blue stain, the secondary degeneration of fiber bundles about the Gasserian ganglion and the secondary degeneration of most of the central bundles of the optic nerve. Unfortunately the application of the anilin blue stain to the brain substance of this case is of less service. For it proves not possible to differentiate convincingly the supposed axis-cylinders from long cell processes of some of the large active neuroglia cells which characterize many parts of the sclerotic regions. However, so far as appearance without differential staining can convince, it is possible to say that at least some axis cylinders, minus myelin, penetrate the sclerotic areas. This would align the case with the cases known as multiple sclerosis.

The finer characters of the lesion are of interest, especially as bearing on the differentiation of gliosis from glioma.

The sclerotic tissue varies strikingly in microscopic structure, although the amount of intercellular substance is everywhere above that of the normal cerebral white matter. The variations are chiefly shown in the number and character of the neuroglia cells which produce the fibrils. The transitions in the mass of the lesion are never abrupt and never so well marked as the transition between the sclerotic tissue and the relatively normal cortex. The neuroglia cells vary in number and size in the sclerotic tissue, just as they do in those focal overgrowths of neuroglia tissue which we know as gliomata.

In places (characteristically along the exterior of the sclerotic tissue), the cells are small, placed at fairly regular intervals, and provided with branched cell-bodies which somewhat recall the characteristic cell bodies of reacting sub-pial neuroglia cells.

In other places (characteristically in the interior of the lesion), the cells are larger (often meriting the name giant cell), placed at smaller intervals (sometimes giving a pavemented appearance to the lesion), and provided with numerous overlapping nuclei which are crowded about the periphery of the cell. The centers of these large cells are homogeneous and finely granular and are provided with a varying number of centrosome-like structures.

In a few foci, there is a third type of cell in which activity seems to be spent on expansion of the cell-body and the production of numerous heavy, branched, and deeply staining processes, which are sometimes frayed at the ends like cut wire-rope.

In places there are remarkable clusters and rows of ependymal cysts, lined with perfectly formed ependymal cells, which are provided with basal bodies and attached cilium-like appendages. These cysts are not of diffuse occurrence but occur particularly in the neighborhood of the posterior horns of the ventricles. Occasionally the cysts are so aligned, between stratified masses of neuroglia coincident in direction with the major axis of the ventricle, that the impression is gained that such accessory cystic spaces are developed along with the ventricle and belong to its ground plan.

Over against these perfectly formed ependymal cysts may be set certain less regular cysts which are perhaps due to the hollowing out of the cytoplasm of some of the giant cells with peripheral nuclei noted above. Such irregular cystic spaces are, however, not common in this tissue.

The gradual variations in cell character above noted, taken together with certain variations in the amount and texture of the intercellular fibrillary substance (often particularly dense about vessels), are not inconsistent with the diagnosis, glioma. There is considerable evidence of tissue destruction throughout the sclerotic tissue in the shape of dense deep masses of pigment-bearing phagocytic cells in the vessel sheaths. The material so laid down is probably derived from the destruction of nerve fibre constituents incident to the lesion, since there is nowhere any sign of necrosis in the sclerotic tissue itself and there is little or no accumulation of phagocytic cells in the overlying cortex or in the pia mater.

IV. SUMMARY.

1. Boy of six and a half years. Measles at three years. One year before death, fell backward down three steps in a cellar, with epistaxis, and possibly bleeding from ear. Afterward "nervous." A month later began to stagger in walking, became gradually deaf and stupid, later blind and dumb. Operation for chronic internal hydrocephalus. Death two days after operation.

2. The autopsy showed sclerosis of the white matter of the occipital, parietal, and temporal lobes on both sides with sclerosis of optic thalami and of small, roughly symmetrical areas in the white matter of the cerebellum.

3. The microscopic examination shows a cellular and fibrillary overgrowth of neuroglia, sharply limited to the white matter. The picture gradually varies from that of masses containing giant cells and few fibrils to that of active fibril-producing cell masses or that of stratified areas of inactive fibrillar gliosis.

4. The lesion involves the destruction of myelin sheaths and considerable axis-cylinder material. The lesion may be described as a multiform gliosis of the white matter with extensive mildly destructive properties. The nutrition of the areas is maintained. The overgrowth of neuroglia substitutes for, and to some extent destroys, the involved tissues, but fails to invade, in the sense of invasion by glioma. The overlying cortex fails to show important changes. The origin of the condition is unknown.

A Study of Brain Infections with the Pneumococcus.

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BOSTON.

Reprinted from The Journal of the American Medical Association, January 6, 1906.

CHICAGO:
PRESS OF THE AMERICAN MEDICAL ASSOCIATION,
ONE HUNDRED AND THREE DEARBORN AVENUE,
1906.

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BOSTON.

A STUDY OF BRAIN INFECTIONS WITH THE PNEUMOCOCCUS.*

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Following is a report of twelve cases of human brain infection with the pneumococcus, together with the results of inoculation of the pneumococcus in the brains of guinea-pigs. Both the human and the experimental material have been used to establish the order and time relations of the acute inflammatory changes. The work is on the lines of our study of encephalitis due to the *Staphylococcus pyogenes aureus,*[1] but was particularly suggested by the case of pneumococcus brain infection (here abstracted as Case 1) reported by Bullard and Sims[2] from this laboratory in 1904.

Profs. W. T. Councilman and F. B. Mallory have looked over the work. On the bacteriologic side we have been much aided by Drs. C. W. Duval and P. A. Lewis, of the hospital staff. We wish to thank Drs. J. H. McCollom, A. L. Mason, G. B. Shattuck, F. H. Williams, C. F. Withington, G. G. Sears, E. M. Holmes, and G.

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* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

* From the Pathological Laboratory of the Boston City Hospital.

[1] "A Study of Acute Hemorrhagic Encephalitis (Staphylococcus pyogenes aureus)." E. E. Southard and C. W. Keene, Amer. Jour. of Med. Sci., March, 1905.

[2] "A Case of Diffuse Encephalitis Showing the Pneumococcus." W. N. Bullard and F. R. Sims, Boston Med. and Surg. Jour., December, 1904.

A. Leland for their clinical notes, and Drs. F. B. Mallory, J. H. Pratt, A. R. Diefendorf, H. C. Low, H. A. Christian, R. L. Thompson, S. B. Wolbach, C. W. Duval, P. A. Lewis, and E. B. Bigelow for their autopsy records. We are ourselves responsible for the histologic work.

Case 1.—This was a case of severe bronchitis in a man of 50 with venereal and alcoholic history.

Clinical Summary.—Cerebral symptoms developed after a month's illness, ushered in by increasing weakness, fever and mild delirium (symptoms on admission). Two days later there appeared flaccid paralysis of the left extremities, with some rigidity on the right, cyanosis, and incontinence. There was gradual failure, with rapid respirations, raised temperature, deepening coma, and death on the seventh day.

Anatomic Summary.—There was acute purulent bronchitis with edema, softening and punctiform hemorrhage involving the greater part of the right cerebral projection system with foci in the left centrum semiovale.

Microscopic Findings.—There were pneumococcus septicemia, slight arteriosclerosis affecting all the organs, acute bronchopneumonia, extensive diffuse encephalitis with hemorrhages and cellular lesions related to the cortical vascular system and confined to the subcortical region. The lesions consisted of accumulations within and surrounding the adventitia of large numbers of mononuclear cells (granule cells), and small numbers of lymphoid and plasma cells, with a few polynuclear neutrophile cells and a few eosinophiles.

There were solution and fatty change of the myelin in the surrounding tissue, and hyperplasia and proliferation of neuroglia cells with formation of numerous astrocytes. There were edema changes in the nerve cells of the cortex, fatty changes in the cord, and early central chromatolysis of the anterior horn cells.

Lanceolate diplococci were present in cultures and were found in and surrounding the cells of the exudate in the lung lesions and in the tissue and granule cells of the brain.

Case 2.—H. H., a boy of 10, was admitted to Dr. J. H. McCollom's service at the south department of the Boston City Hospital, July 13, 1898.

History.—He had measles and whooping cough at 5, mumps at 8 years of age. He was well the day before entrance. He ate a heavy lunch before bedtime, and had headache and vomiting during the night. He "slept" till next afternoon, when respirations became stertorous. The boy was admitted to the hospital in coma, with stertorous and labored breathing, profuse nasal discharge, dilated pupils not reacting to light, râles throughout the chest, small, high tension, rapid pulse, tense and prominent abdomen, exaggerated patellar and plantar reflexes, anesthesia of extremities and marked muscular snsibility to pain. He was catheterized and the urine showed a large trace of albumin. The coma continued. The patient vomited twice. Death occurred about one hour after midnight.

Clinical Summary.—A boy of 10 goes to bed one evening after a heavy lunch, vomits and has headache in the night, sleeps all day, is admitted to hospital in coma and dies twelve hours later, less than twenty-eight hours after the onset of the symptoms.

Anatomic Findings.—The autopsy, performed by Dr. F. B. Mallory, July 14, 1898, showed: Pia injected and edematous; no increase of fluid in ventricles. Small areas of hemorrhage and beginning softening were found in the cerebral cortex beneath the olfactory lobes, along the inner side of the right temporal lobe, and in the right side of the pons. No area exceeded 1 cm. in diameter.

Anatomic Diagnoses.—Pneumonia in middle lobe of right lung and base of left lower lobe. Petechial hemorrhages in skin over chest. Hemorrhages in mucous membrane of bladder. Hemorrhages in cerebral cortex.

Microscopic Findings.—Cultures from the brain and kidney showed a variety of organisms, including the pneumococcus; from lung, pneumococcus; from heart's blood, liver and spleen, sterile.

The pia mater over the areas of softening showed considerable edema, with polynuclear leucocytes and mononuclear cells in about equal numbers. Leucocytes wandered freely through the cerebral tissue. The subpial layer of neuroglia was thin. The areas of softening consisted of small hemorrhages, with polynuclear leucocytes, some of which contained numerous lanceolate diplococci. In some cases the free blood was confined to the adventitial clefts. Lesions of the arteries were rare. The walls of the small veins were sometimes obscured by masses of leucocytes; but there was no thrombosis or lifting of endothelium by exudate.

Case 3.—W. B., a man of 70, was admitted to Dr. G. G. Sears' service at the Boston City Hospital, Sept. 26, 1898.

History.—Three or more days before admission his face had begun to swell, burn and itch, and the lids swelled so that he could not see. Temperature was 101 F. He was slightly delirious, but could be aroused to complain of swelling ankles, shortness of breath, palpitation and dizziness. He was said to have had "shocks" eight years and one year ago. Thorax, abdomen and extremities were negative. The urine showed a trace of albumin and numerous fine granular casts, with a few cellular elements. The patient died four days later. He fell out of bed during delirium the night of entrance and cut a gash in the left occiput. The delirium continued. Three days after entrance the temperature began to rise and the pulse to fail, the respirations became stertorous. Death followed the next morning.

Clinical Summary.—Man of 70, with heart symptoms and kidney disease and a history of paralytic shocks, dies in delirium a week or more after the onset of facial erysipelas.

Anatomic Findings.—The autopsy, performed by Dr. J. H. Pratt, Sept. 30, 1898, showed:

Dura distended over cortex and convolutions flattened. Beneath the dura over the left parietal lobe there was a thin layer of coagulated blood. On the cortex beneath the arachnoid were scattered areas of greenish purulent exudate, especially marked over the frontal lobes, and also over the cerebellum. The base was not involved. The ventricles were dilated, and contained a small amount of clear serous fluid. The walls were not softened.

Anatomic Diagnoses.—Acute purulent meningitis. Old tuberculous focus in lung. Edema and congestion of lungs. Acute bronchitis. Chronic obliterative appendicitis. Chronic interstitial nephritis. Coronary endarteritis. General arteriosclerosis. Chronic interstitial orchitis.

Microscopic Findings.—Cultures from heart's blood, liver, meninges and lateral ventricles showed pneumococcus. Spleen and kidneys were sterile. Sections of cortex presented a constant picture. The exudate consisted of polynuclear leucocytes and mononuclear cells (proportion between 5 and 10 to 1) free in the pial spaces. A few spaces in the middle zone of the pia contained only granular coagulum. Much round-meshed fibrin was deposited in small foci about the small veins and along the inner zone of the pia. The elastica of the small arteries was penetrated by the polynuclear cells, which lay in spaces beneath the endothelium (or in clefts of the elastica) together with mononuclear cells.

The layer of subpial glia was dense and fine-meshed. Eccentrically swollen glia cells, with a small number of embracing fibrils, were frequent. There were a few polynuclear leucocytes in the nerve-cell layers, as a rule near capillaries.

Case 4.—T. W., a man of 44, was admitted to Dr. G. B. Shattuck's service at the Boston City Hospital Oct. 29, 1898.

History.—He had breakbone fever in Baltimore at the age of 19. Right chest was tapped for pleurisy one year before entrance. There was severe pain in the lower left chest four days before entrance. There were cough, orthopnea, insomnia and sweating. At entrance there were signs of effusion in the left chest; there were two dry taps. About twelve days after admission, the patient began to have severe cough and irregular temperature, with persistence of signs in chest and increasing pallor. Two days later he complained of pains in the eyes and severe headache and became semicomatose. The area of bronchial breathing increased. A friction-like murmur developed in the lower heart area. Death occurred November 14, without recovery from coma.

Clinical Summary.—Man of 44, with history of pleurisy of a year's standing, develops a fresh attack, in the course of which, sixteen days after onset, twelve days after admission to hospital, he became much worse. There were pains in the eyes, headache, coma. Death occurred three weeks after onset of symptoms and four days after exacerbation of symptoms.

Anatomic Findings.—The autopsy, performed by Drs. J. H. Pratt and Diefendorf, Nov. 14, 1898, three hours after death, showed:

Head (Dr. Diefendorf): Pia showed over vertex and base a slight haziness, and along longitudinal fissure on both hemispheres, several areas from 1 to 3 cm. in diameter, greenish yellow in color, on section showing thickness of from 1 to 4 mm., not exuding but rather firm. A few similar areas were scattered in the sulci over the frontal and parietal lobes. A similar but more extensive exudate was found in the interpeduncular space, along the ventral surface of pons and medulla, and at the lateral margins of cerebellum.

Brain tissue was firm. On section a greenish yellow exudate was found in the posterior horns of the latter ventricles, and in the floor of the third ventricle. Ependyma elsewhere was clear. Vessels at base were negative. Middle ears were normal.

Cord: On puncture of the dura of the lumbar cord there escaped a clear fluid with several patches of greenish yellow color. This exudate was found along the entire extent of the cord on the right posterior aspect, mostly in flakes, but in places as a rather thick layer, 1x2 cm. in breadth and length, and 5 mm. in thickness.

Anatomic Diagnoses.—Acute purulent cerebrospinal meningitis. Fibrinopurulent encysted pleurisy. Serofibrinous pericarditis. Chronic verrucose endocarditis. Old fibrous obliterative pleurisy. Hydrocele. Parenchymatous degeneration of liver and kidney. Fatty degeneration of kidney. Fatty degeneration of aorta. Acute fibrinopurulent mediastinitis.

Microscopic Fndings.—Cultures from heart's blood, pericardium, pleura and meninges, showed pneumococcus. Spleen and liver gave *B. coli;* kidney was negative.

The meningeal exudate varied in different places in the proportion of polynuclear leucocytes to mononuclear cells. Everywere there were more mononuclear cells than leucocytes. In the wide sulcal space the chief cell found was the phagocyte laden with polynuclear leucocytes. There was little fibrin except near the veins. Vascular lesions were not prominent over the cerebrum and cerebellum, but lifting of endothelium by exudative cells was found in the small vessels of the spinal pia mater.

The subpial glia was coarse, even and regular. Behind the fibrillar layer were numerous eccentrically swollen glia cells, often with two or even three nuclei. Some of these cells showed fibrillæ in close apposition to processes. Leucocytes penetrated the cortex somewhat freely and occurred singly in the deeper nerve-cell layers.

Case 5.—R. A. a man of 35, was admitted to Dr. A. L. Mason's service at the Boston City Hospital, April 15, 1900.

History.—Chills and cough with yellowish-white sputum had set in six days before entrance. There were pain in the right chest, rise of temperature and free perspiration. He had been in bed four days. He was admitted in delirium, with rusty sputum and with signs of pneumonia in the right chest. Knee jerks and plantar reflexes were normal. There was inflammation of the skin about the shoulders. On April 17 the right forefinger became inflamed and the swelling spread to the dorsum of the hand. An incision was made and pus withdrawn. By April 22, the morning temperature had become normal, but began to rise again irregularly. On the afternoon of April 25 the patient suddenly became much worse, coughed spasmodically and showed dyspnea, cyanosis and delirium. There was stiffness of the neck without retraction. Meantime the inflammation in the hand had largely subsided. The next day Cheyne-Stokes respiration set in, the pupils dilated, the knee jerks became slight and the plantar reflex was lost on the right side. Death occurred in less than twenty-four hours after exacerbation of the symptoms.

Clinical Summary.—Man of 35, with history of excess in alcohol, shows signs of pneumonia in the right chest. Two days after admission (eight days after onset of symptoms) inflammation of right forefinger and hand set in. Incisions were made to relieve the swelling and were followed by general improvement. Sixteen days after onset of symptoms and ten days after admission, a sudden relapse occurred, with spasmodic cough, stiffness of neck and delirium. Death occurred the next day.

Anatomic Findings.—The autopsy, performed by Dr. H. C. Low April 27, 1900, showed:

No congestion of the dura which was not adherent or thickened. The sinuses were distended by fluid blood. The pia was rather opaque, and between it and the brain a greenish-yellow material, thick and viscid in appearance, was visible. The veins were very much congested. This appearance was most pronounced on either side of the median line. decreasing toward the sides and on the inner surface of the frontal lobes, where it was marked only along the course of the vessels. The vessels at the base were congested and the entire cerebellum was covered by the exudation. The ventricles did not contain an excess of fluid, but the fluid in the lateral ventricles was slightly opaque. Middle ears were normal.

Anatomic Diagnoses.—Acute purulent meningitis. Acute pericarditis. Acute splenitis. Organizing lobar pneumonia. Acute endocarditis (aortic). Septic wound of hand. Ascites. Acute fibrinous pleurisy. Acute bronchitis.

Microscopic Findings.—Cultures from heart's blood, left lateral ventricle and lungs, showed pneumococcus. The right lung showed streptococcus. Spleen, liver, gall bladder and kidney were sterile. The picture varied in different parts of the pia mater. The zone adjacent to the nerve tissue, the perivascular region and certain spaces in the middle third of the pia mater contained much fibrin and polynuclear leucocytes which far outnumbered the mononuclear cells. In the wide sulcal space the mononuclear cells equalled or excelled the leucocytes in number. The large sulcal veins showed infiltration of the intima, with polynuclear leucocytes and extensive increase in the intimal cells. The subpial glia was scanty. A few glia cells with two nuclei occurred; there was no increase in fibrils. Polynuclear leucocytes were found about the small vessels, singly free in the cortex, but seldom in the underlying white matter.

Case 6.—J. H., a man of 47, a teamster and a drunkard, was admitted to Dr. G. G. Sears' service at the Boston City Hospital, Jan. 6, 1901.

History.—Four days before entrance to hospital he fell on his back, but was able to move about afterward, though drunk. He took to bed for a short while. He complained two days before entrance of pain in the head and back of the neck. He ate nothing for twenty-four hours before entrance. At entrance there was delirium, restlessness and tremor of extended fingers. Pupils were equal, with normal light reaction. Knee jerks were lively. The urine showed .25 albumin and many (chiefly granular and epithelial) casts. Physical examination was chiefly negative. The next day deep coma had set in and death occurred January 8.

Clinical Summary.—Man of 47, dies in coma seven days after a fall.

Anatomic Findings.—The autopsy, performed by Dr. H. A. Christian, Jan. 9, 1901, showed:

Head: Dura is very tense. When opened there was a gush of grayish turbid fluid, and the dura collapsed to a considerable extent. The surface of the cerebrum and cerebellum was covered with greenish-yellow pus and fibrin. This was everywhere most marked along the course of the larger blood vessels, which appeared as dark red stripes bordered with greenish yellow. It was most prominent over the vertex of the cerebrum, along the Sylvian fissure, over the superior surface of the cerebellum and at the base in the area bounded by the circle of Willis, and along the olfactory nerves. The exudate was less abundant at the base than at the vertex. Over the convolutions where the exudate was thin, many small injected blood vessels could be seen. The superior longitudinal, lateral and superior and inferior petrosal sinuses contained fluid blood and were normal.

Smears from the exudate showed pus cells and many diplococci, some lanceolate, and a few large bacilli. Many of these were within the pus cells. The diplococci failed to show definite capsules when stained by Welch's method, though they were indicated in some places. The organisms stained by Gram's method. The middle ears were normal.

Spinal cord: Dura was normal, but distended. Over the posterior surface of the cord there was much yellowish pus and fibrin similar to that on the surface of the brain. Over the posterior surface of the cord the long spinal vessels were much distended, appearing as small sinuous red cords.

Anatomic Diagnoses.—Chronic fibrous pleuritis. Chronic fibrous pericarditis (milk patches). Hypertrophy and dilatation of heart. Fatty degeneration of heart. One accessory coronary artery. Congestion and edema of lungs. Chronic passive congestion of liver. Acute nephritis. Hydrocele and varicocele. Slight chronic aortitis. Fatty degeneration of skeletal muscles. Acute cerebrospinal leptomeningitis.

Microscopic Findings.—Cultures from pia mater gave pneumococcus pure. The kidney gave pneumococcus and *Staphylococcus pyogenes aureus.* The lung contained streptococcus, *Staphylococcus aureus* and *B. proteus.* Liver and spleen were sterile. The meningeal exudate was evenly cellular, except about the veins near the nerve tissue where fibrin was developed. The cells were almost all polynuclear leucocytes. In the adventitiæ of the veins, however, the proportion of mononuclear cells rose to 1 in 10 or 20. In the veins there were numerous minute mural thrombi, largely covered in by endothelium. The subpial glia was thin, but close-meshed. The outer layers of cortex contained numerous neuroglia fibrils of fine, even diameter. There were a few free leucocytes in the outer layers, caught singly sometimes in ameboid shapes. Mitoses regarded as in neuroglia cells occurred in the subpial layer internal to the dense sheet of fibrillæ, also occasionally in the layer of small pyramids. The nerve cells were pigmented. Cells occupying the site of satellite cells were caught in mitosis in several places; but in general there was slight evidence of increase in number of these cells.

Case 7.—W. N., a man of 58, was admitted to Dr. F. H. Williams' service at the Boston City Hospital, Jan. 21, 1901.

History.—He had had cough and expectoration six or seven weeks before entrance. Chills and backache set in 6 days before entrance. He had had headache for 4 days before entrance. At entrance there were shooting pains in various parts of the body, skin and scleræ were a little yellow, and ears and lips a little cyanotic. The pupils were small and slightly irregular, reacting sluggishly to light. There was radial arteriosclerosis. Emphysema was present and râles more marked at right base; there were also an area of dulness, increased fremitus, and bronchial breathing at the right base. The abdomen was rigid and tympanitic. The knee jerks and plantar reflexes were normal. The discomfort from the pain in the side, distension of abdomen, and frequent catheterization persisted till January 24, when late in the evening the pulse became thready, respiration labored, and the skin cyanotic. Death occurred five hours later, January 25.

Clinical Summary.—Man of 58, arteriosclerotic, with history of six or seven weeks' bronchitis, and less than a week of chills, backache and headache, dies three days after entrance in the course of pneumonia of the right side.

Anatomic Findings.—The autopsy, performed by Dr. H. A. Christian, Jan. 26, 1901, showed:

Head: Superior longitudinal findings were normal. The surface of the cerebrum and cerebellum was greenish, opaque and gelatinous, and dotted with numerous whitish areas about 1 mm. in diameter. The pia was thickened everywhere over the upper surface and tore with some difficulty. Smears made from under surface of the pia showed many pus cells and Gram staining diplococci. Many of the diplococci were lanceolate and when stained by Welch's method showed fairly distinct capsules. The ventricles contained a small amount of normal fluid. The brain substance appeared normal. The middle ears were normal.

Anatomic Diagnoses.—Acute leptomeningitis. Jaundice (universal). Chronic fibrous pleuritis. Acute serofibrinous pleuritis. Fatty degeneration and brown atrophy of heart. Lobar pneumonia. Acute bronchitis. Acute degeneration of kidney. Slight chronic aortitis.

Microscopic Findings.—Cultures from the under surface of pia mater, lung, liver and kidney showed pneumococcus. The meninges were wide, but contained few exudative cells except in the inner zone and about the veins. In both regions the mononuclear cells surpassed the polynuclear leucocytes in number. In the inner zone of the pia there was considerable fibrin inclosing leucocytes, many of which stain poorly. The mononuclear cells in the adventitiæ of the veins frequently had nuclei indented on one side. The intimal cells of the arteries and veins were swollen and increased in number. An occasional arteriole had its lumen seven-eighths narrowed by swollen intimal cells.

The subpial layer showed a thin, dense sheet of neuroglia. The cortex showed numerous fibrils as far inward as the outer limits of the layer of large pyramidal cells. Scattered through the cortex were neuroglia cells containing pigment. There was a slight increase of glia fibrils in parts of the underlying white matter. The neuroglia cells failed to show acute changes. The vessels of the cortex were engorged with blood. In their sheaths were a few mononuclear cells, but seldom a polynuclear leucocyte. The nerve cells stained well, were often overpigmented, and were attended by numerous satellite cells, some of which showed a tendency to be metachromatic.

CASE 8.—W. M., a man of 37, was admitted to Dr. C. F. Withington's service at the Boston City Hospital, Feb. 26, 1903.

History.—He had had chills, fever, pain in left chest, cough, and dark expectoration for a week before entrance. There were pneumonia and pleurisy on the left side. Pupils were normal. Knee jerks were normal. The plantar reflexes were exaggerated. The urine showed a few hyaline casts. Death occurred the day after entrance.

Clinical Summary.—Man of 37, with history of "bronchitis" for years, dies one day after entrance to hospital, eight days after onset of symptoms of pneumonia of left side.

Anatomic Findings.—The autopsy, performed by Dr. E. E. Southard, Feb. 28, 1903, showed:

Head: Dura was tense and of normal color. Arachnoidal villi were moderately developed. The pia was of a green-gray color, more marked over the frontoparietal and cerebellar regions and at the base. The greenish color in places was obscured by edema, which in the parietal and occipital regions was marked. There were pneumococci in the smear from the exudate. The convolutions were not markedly flattened. The ventricles were normal and contained a normal amount of fluid. Substance in the gross was normal. The sinuses contained fluid blood and long shreds of chicken-fat clot. The middle ears were normal.

Anatomic Diagnoses.—Lobar pneumonia (gray hepatization). Acute leptomeningitis. Acute fibrinopurulent pericarditis. Chronic adhesive pleuritis. Chronic adhesive pericarditis. General arteriosclerosis.

Microscopic Findings.—Cultures from heart's blood, lung, spleen and brain showed pneumococcus. The exudate in the pia mater was chiefly cellular, but in certain wide spaces in the middle zone it consisted of a granular coagulum. About the small veins and along the inner zone considerable fibrin was developed. The cells were mainly polynuclear leucocytes; but mononuclear cells occurred in the proportion of 1 to 10 or 20, or in a lesser proportion. The small veins showed an increase of intimal cells in compact layers penetrated by polynuclear leucocytes. The small arteries had their intimæ lifted by polynuclear leucocytes and mononuclear cells. The subpial layer showed considerable neuroglia in a loose sheet, which in places was made looser by edema. A few polynuclear leucocytes were found free in the outer portion of the layer of small pyramids. It was easy to mistake altered neuroglia cells of the edematous outer layers for polynuclear leucocytes. Pigmented neuroglia cells and considerable numbers of satellite cells occurred.

CASE 9.—G. G., a man of 25, was admitted to Dr. C. F.

Withington's service at the Boston City Hospital, May 25, 1904.

History.—He had received a head injury on board ship. He lay unconscious for some time in a hospital in Porto Rico, but recovered. He had headache for four days previous to entrance, and there was unconsciousness for two days. On entrance he was restless and cried out when touched. He lay on his side, with the legs drawn up. His neck was stiff and retracted. Passive flexion was painful. The abdomen was slightly retracted. The knee jerks and plantar reflexes were exaggerated. Kernig's sign and Babinski's sign were present on both sides. There was *tâche cérébrale.* There was incontinence of feces, and the restless delirium persisted. Two days after entrance the pupils began to react sluggishly to light, and two days later the head was retracted to the left, with conjugate deviation of the eyes to the left. The extremities were somewhat spastic. Kernig's sign became less marked, and Babinski's sign was lost. Death occurred five days after entrance.

Clinical Summary.—Man of 25, with obscure history of previous head injury, has headache four days and is unconscious two days before entrance. Death occurs six days later, 10 days from onset of symptoms of meningitis.

Anatomic Findings.—The autopsy was performed by Drs. R. L. Thompson and E. E. Southard 32 hours after death.

Head: The scalp and cranium were normal. The sphenoidal sinus contained a small amount of clear gelatinous material. The other sinuses were normal. The middle ears were normal. The right cavity contained a little clear gelatinous material resembling that in the sphenoidal sinus. The pores of the right cribriform plate contained fibrinous pus in continuity with the exudate about the right olfactory lobe. The nasal cavities were clean.

Brain: Weight, 1,350 gms. The dura was slightly thickened, clung lightly to pia on peeling, but there were no adhesions. The sinuses of the dura contained cruor clot. The pia was tense, injected and a little sticky. The tissues about a few large sulcal veins were infiltrated with greenish, stringy pus. The frankly purulent areas of the vertex were never over 2 cm. in diameter and lay at varying distances within 6 cm. therefrom. There were a few subpial collections of pus over the cerebellum, especially near the brachium. A few of the arachnoidal villi were injected and a little more plastic than usual. The tissues about the basal veins, the chiasm and the infundibulum showed a deep layer of moist, stringy, greenish pus, apparently all within the pia. Both Sylvian fissures showed an extension of the exudate for 3 cm. The gyri were flattened, firm, a little plastic, of homogeneous consistence and slightly pinker than usual. The cortical markings were everywhere distinct. Substance clung to the knife on section. The puncta cruenta in various places in the white matter were unusually distinct; and, opposite the left frontal cortex, there were numerous punctiform hemorrhages in very clinging edematous substance. In the middle of this area was a focus 1 cm. in diameter composed of greenish fibrinous pus surrounded by a ragged injected wall. The right olfactory lobe was yellower and softer than the left and was glued in an exudate continuous with the exudate at the base. All the ventricles contained greenish fluid containing fibrin and grumous coagulum. There was no normal ependyma remaining. The exudate could be removed only by scraping and extends for from 1 to 2 mm. into subependymal tissue. The floors of the lateral and fourth ventricles looked like the walls of abscess cavities. The medulla was buried in pus filling the pial meshes. The substance was a little softened and over injected.

Cord: The dura was thick, a little brawny, and internally roughened. It peeled from the pia with slight difficulty. The meshes of the pia were distended with pus resembling that found in the cranium. The outermost layers of the pia were rather edematous, which made the exudate look more glassy than the cranial exudate. On section the cord appeared moister than normal and the pial vessels were markedly injected, resembling in places so many red spokes let in from the pial rim. The larger veins were not much injected. The exudate in places, notably about the cauda equina, was very thick and with the included nerves might measure from 0.75 to 1 cm.

Anatomic Diagnoses.—There were edema and congestion of the lungs, edema of the kidneys and acute splenitis. There was cerebrospinal meningitis, with focal abscess, encephalitis and pyocephalus. There was an exudate about the degenerating right olfactory lobe, with slight inflammatory reaction by extension in the cerebral and spinal dura.

Microscopic Findings.—Cultures from heart's blood and brain gave pneumococcus; from right lung, staphylococci; from left lung, *Streptococcus pyogenes*; from liver, *B. coli, B. proteus, etc.*; from spleen, *B. coli.* Cultures from the kidney were sterile. The meningeal exudate was largely cellular. The centers of the clefts were occupied by polynuclear leucocytes and an equal number of mononuclear cells. Near the vessels the mononuclear cells were more frequent and were often vacuolated or phagocytic for polynuclear leucocytes. Fibrin occurred in masses of irregular distribution, as well as about the veins. The arteries showed a minor degree of intimal swelling, with occasional included cells. The subpial neuroglia showed numerous swollen cells and a few mitoses. There was an increase of fibrils in the subpial layer. The cerebellum of this case showed an exudate much richer in large leucocyte-containing phagocytes than the cerebral exudate, and neuroglia-cell mitoses were fairly frequent in the molecular layer. Polynuclear leucocytes wandered freely in the cortex.

Case 10.—E. V., a man of 48, was admitted to Dr. C. F.

Withington's service at the Boston City Hospital, Feb. 17, 1905.

History.—There was a history of excess in alcohol. He had rheumatism 5 years before entrance. Two days before entrance he parted from a friend at 10:55 p. m., intoxicated but without symptoms of illness. At 11:10 p. m. the man was brought to the relief station with a story of a fall and injury to the head. He was discharged as well the next morning. He was dazed on reaching home, and had pain on the right side of the head. Delirium set in at 10 p. m. February 16. On entrance respiration was rapid and noisy. There was ecchymosis about the left eye. Râles were more marked and respiration more marked in the right back; pulse was rapid and knee jerks equal; Kernig's sign and Babinski's sign were absent. Leucocytosis was 32,600. The delirium continued. By 9:30 the next evening right hemiplegia had developed, with Kernig's sign and Babinski's sign. Death occurred 11 hours later.

Clinical Summary.—Man of 48, alcoholic, was brought to Relief Hospital one night with contusion of face and discharged next morning. He was dazed next day, and delirium was present in the evening. He entered hospital with signs in right lung; hemiplegia occurred on evening of second day, about 70 hours after original trouble. Death occurred eleven and one-fourth hours later.

Anatomic Findings.—The autopsy was performed by Drs. E. B. Bigelow and P. A. Lewis 23 hours after death and showed:

Head: The scalp was rather thick and loose, with a moderate amount of fluid blood beneath the lateral portions, particularly on the left. The calvarium was thick and moderately dense; the dura mater was loose. Convolutions could not be made out through the membranes. Everywhere beneath the dura and still more beneath the pia mater there was an abundance of yellow, tenacious, fibrinopurulent exudate. The distribution was quite even, although there was slightly more over the vertex than at the base. The ventricles contained a considerable amount of clear fluid, with a flocculent yellow precipitate. Section showed a firm, moist surface; the color was rather a dull pinkish-white. The puncta cruenta were well marked. The exudate extended along the trunk of the cranial nerves for a moderate distance. The Gasserian ganglia were infiltrated with pus. The middle ears were normal, and the upper nasal passages seemed normal.

The spinal canal contained a considerable amount of fibrinopurulent fluid. The cord was firm. The vessels were injected.

Anatomic Diagnoses.—Bronchopneumonia. Nephritis. Arteriosclerosis. Cirrhosis of liver. Old infarct of spleen. Acute cerebrospinal meningitis.

Microscopic Findings.—Cultures from heart's blood, spleen and brain were sterile. One culture from lateral ventricle was contaminated with *Staphylococcus albus.* Drs. Duval and

Lewis were able to recover the pneumococcus from a rabbit into which pus from the ventricle was injected. The meningeal exudate was composed largely of cells; the polynuclear leucocytes slightly outnumbered the mononuclear cells. Fibrin occurred about the small veins. The endothelium of some arteries was lifted by a deposit of cells, chiefly polynuclear leucocytes. The subpial neuroglia was fairly dense but edematous. There was no evidence of acute neuroglia cell changes.

CASE 11.—J. M., a boy of 10, was admitted to the aural service of Dr. E. M. Holmes at the Boston City Hospital Sept. 27, 1904.

History.—Two weeks before he was seen in the outpatient department with bilateral otitis media. A right mastoid operation was performed September 29 by Dr. Holmes, but was stopped on account of hemorrhage. The temperature remained high. The patient vomited sometimes after eating. Two weeks after entrance a second mastoid operation was done on the left side by Dr. G. A. Leland. After this the temperature fell, but five days later right facial paralysis developed with well-marked *risus sardonicus* on left. There were ptosis of the left eyelid, slight horizontal nystagmus, convergent strabismus on right, slight rigidity of neck, and Kernig's sign. Toward evening, twitchings of the left side of the face developed and the paralysis gradually disappeared. Death occurred the next day.

Clinical Summary.—Boy of 10, with bilateral otitis media of unknown duration (over two weeks), on whom mastoid operations were performed, death occurring three weeks after admission and one week after a second operation.

Anatomic Findings.—The autopsy was performed by Dr C. W. Duval 27 hours after death and showed:

Head: The scalp and calvarium were normal. Behind the left ear was a surgical incision 5 cm. in length, running parallel with the external ear and directly over McEwen's triangle. Six or eight stitches held it together. The dura was non-adherent except along petrous portion of the left temporal bone. The sinuses contained fluid blood. The whole of the left hemisphere beneath the pia was covered with thick, greenish-yellow pus. Parts of the cortex beneath this pus showed marked depressions. The right hemisphere was congested, and the convolutions and sulci obliterated. The cortical substance was quite firm in consistence.

Anatomic Diagnoses.—Chronic pachymeningitis. Purulent leptomeningitis. Acute encephalitis. Mastoiditis (acute and chronic). Edema and congestion of the brain. Chronic pericarditis.

Microscopic Findings.—Cultures from heart's blood, liver, spleen and meninges were sterile. Numerous Gram-staining, lancet-shaped diplococci with capsules were found in smears from meninges. The microscopic picture in the cortex was mixed. There was an exudate of small mononuclear cells, some of them lymphocytes, about some veins. Besides this, there was a deep layer of fibrin with polynuclear leucocytes enmeshed, and there were foci composed chiefly of polynuclear leucocytes. A great portion of the acute exudate failed to stain well. Vacuolated and leucocyte-containing mononuclear cells were frequent. The small arteries showed swelling without proliferation of endothelium. The subpial neuroglia showed mitoses and eccentrically swollen cells. There were a few newly-formed fibrils. Leucocytes did not wander freely into the nerve substance.

Case 12.—J. M., a woman of 45, entered the aural service of Dr. G. A. Leland, April 18, 1905.

History.—She had had pain in the right ear for three weeks. The evening before entrance coma set in. At entrance there was prostration. Temperature was 102.6; respiration, 50; pulse, 120. The right pupil was larger than the left; both pupils were sluggish to light. The retinæ were congested and there was paralysis of the right sixth and seventh nerves. There were diminished sensation of right side of body, stiffness of neck with pain on pressure, absence of knee jerks, a suspicion of Kernig's sign on both sides and mastoid tenderness. A mastoid operation was done at midnight. Death occurred 10 hours later.

Clinical Summary.—A woman of 45, with history of pain in right ear for three weeks, becomes comatose and shows sensory and motor paralyses of right side of body. Death occurred 10 hours after mastoid exploration.

Anatomic Findings.—The autopsy was performed by Dr. S. B. Wolbach 1 hour after death and was limited to the head.

There was a wound of right mastoid operation. The subcutaneous tissue of the scalp was slightly edematous. The calvarium was of average thickness and density. The dura was normal. The right superior longitudinal, the occipital, superior and inferior petrosal sinuses and right lateral sinus were normal and contained liquid blood and cruor clot. In the left lateral sinus at the torcular Herophili there was a thrombus beginning at the junction of the right and left lateral sinuses and extending laterally to the left for a distance of 1 cm. This thrombus was grayish-pink in color, friable and firmly attached to the walls of the sinuses. Close to the jugular foramen, and 6 cm. from the torcular, there was another similar thrombus 1.5 cm. in length. Between the dura and the temporal bone there was a thin layer of clotted blood covering an area about 7 cm. in diameter. Along the course of the vessels of both hemispheres there was a grayish-yellow exudate, thickest at the fissure of Sylvius and diminishing toward the median fissure. This exudate was subpial, approximately equal in amount on both sides and extended to the median fissure on both sides. The base of the brain was covered with a similar, rather more abundant deposit, thickest at the beginning of the fissures of Sylvius about the infundibuliform process and third nerve. The entire surface of the cerebellum was covered with a similar exudate. The consistency of the brain seemed good, and it cut with ease. The cut surfaces were rather moist; puncta cruenta were prominent as oozing points. Each ventricle contained about 5 c.c. of yellowish, cloudy liquid. At each posterior horn and at each lateral horn there was a small quantity of thick, greenish-yellow puriform matter. The pineal body was represented by a cyst 1 cm. in diameter. The exudate on the surface of the cerebellum and geniculate bodies was continuous beneath the splenium with a similar exudate present in the velum interposition about the pineal body. Section of the basal and centrum semiovale showed nothing abnormal. The pons and medulla were normal. The exudate extended downward from the pons, medulla and cord as far as could be seen through the foramen magnum. The left middle ear was normal. In the right middle ear, the upper anterior half of the membrane tympani was destroyed. The cavities of the middle ear and antrum were filled with yellowish-red granulations. The incus lay free in the cavity of the middle ear. The malleus was held loosely in position. The cells of the surrounding cancellous bone contained a thick, clear, yellowish fluid. The sphenoidal sinus contained a quantity of gelatinous, yellowish material. Cover-glass preparations from the exudate at the base of the brain and from that in the ventricles showed many lanceolated, Gram-staining diplococci.

Anatomic Diagnoses.—Pneumococcus meningitis. Thrombosis of left lateral sinus. Chronic otitis media. Infection of sphenoidal sinus. Mastoid operation.

Microscopic Findings.—Cultures from the meninges showed pneumococcus. The meningeal exudate varied. In some places polynuclear leucocytes surpassed the mononuclear elements in number, but in most places mononuclear cells, chiefly phagocytic for polynuclear leucocytes, occurred in large numbers. Proliferation of the intima and infiltration of the walls of the veins and exudative lifting of the arterial intimæ were found. Occasionally a small vein was found completely occluded by a fresh leucocytic thrombus. The subpial neuroglia was fairly dense. Polynuclear leucocytes were sometimes found in the cortex and wandering freely in subependymal tissues.

GENERAL CLINICAL SUMMARY.

Eleven patients were male, one (Case 12) female. The youngest were two boys of 10 (Cases 2 and 11), the oldest a man of 70 (Case 3). The average age was 43.

Seven patients were between 35 and 50, 3 under 35, two over 50.

Two cases followed inflammation of the middle ear (Cases 11 and 12). The other ten cases showed no inflammation of the middle ear.

Two (Cases 6 and 10) gave a history of trauma while drunk. The patient in Case 9 is said to have recovered from head injuries.

Four cases gave history of excess in alcohol (Cases 1, 5, 6 and 10).

Four cases gave history of pyogenic infections of long standing, three (Cases 1, 7, 8) of chronic bronchitis, one (Case 4) of old pleurisy.

The character of onset varies. Cases 11 and 12 were the outcome of neglected otitis media. In cases 6 and 10 the onset was probably rapid, but obscured by alcoholism. Cases 7 and 8 were incidents of pneumonia, Case 5 of unresolved pneumonia, Case 4 of pleurisy, Case 3 of erysipelas. Case 2 was fulminant.

The durations of the acute symptoms and of the symptoms ascribable to cerebral lesions may be assigned (subject to the usual reservations) as given in the accompanying table.

The cases may be characterized briefly as follows:

Cases 11 and 12 were clinically clear: otitis media and sequelæ. Of the other cases, 1, 2, 9, 10 and perhaps 6 could be regarded in life as showing cerebral symptoms, and Cases 4 and 5 gave somewhat doubtful evidence in life of the lesions afterward discovered. Cases 7 and 8 could scarcely be more definitely labeled than as cases of severe pneumonia. Case 3 was apparently not more than a septicemia.

	Duration of acute symptoms.	Duration of cerebral symptoms.
Case 1.	5 weeks	1 week.
Case 2.	28 hours	28 hours.
Case 3.	1 week	1 week.
Case 4.	3 weeks	4 days.
Case 5.	17 days	1 day.
Case 6.	1 week	1 week.
Case 7.	7 to 8 weeks	pneumonia, 10 days.
Case 8.	8 days	pneumonia, 8 days.
Case 9.	10 days	10 days.
Case 10.	81 hours	11 hours.
Case 11.	Over 5 weeks	1 day.
Case 12.	Over 3 weeks	1 day.

GENERAL ANATOMIC SUMMARY.

The brain lesions varied in character and distribution. The lesions affected meninges, ventricles, or the nerve tissue itself.

Meningeal lesions were found in all cases except 1 and 2. The meningeal exudate was greenish or yellowish and contained, as a rule, much fibrin. The exudate was always deeper in the sulci and could be found there in discontinuous sheets. The upper surface of the cerebrum (especially along the vertex and over the frontal region) and the upper surface or sides of the cerebellum showed exudate in all our meningeal cases. The cisternæ and pial tissues at the base, as a rule, were filled with pus; but Cases 3, 7 and 11 (an otitic case) failed to show involvement of the base.

The cases which failed to show involvement of the base failed also to show pus in the ventricles. Case 8 also showed no involvement of the ventricles. The ventricles, as a rule, were all equally involved. The exudate varied from opaque to turbid or flocculent. Although the exudate was elsewhere fluid, single drops of fibrinous pus drained into the posterior cornua of the lateral ventricles. The floors and recesses of the ventricles more frequently showed pus than the roofs and free non-vascular parts. The most destructive suppuration in the ventricles was found in Case 9.

The lesions of the brain substance were various. Eight cases showed no focal lesion of the substance in the gross. Cases 1, 2, 9 and 11 showed acute red softening. Case 9 showed a small abscess. The areas of central encephalitis showed distinct and numerous puncta cruenta and punctiform hemorrhages in the midst of tissue pinker than normal, plastic or friable and edematous.

The spinal cord was affected in those cases in which the tissues at the base showed pus. The pus in the cord membranes occurred frequently in the same discontinuous sheets characteristic of the cortical exudate.

The dura mater was occasionally distended. The venous sinuses, as a rule, contained cruor clots. Case 12 showed sinus thrombosis on the side opposite to the mastoid operation. Cases 11 and 12 were infectious, both of otitic origin. In the other ten cases the middle ears were normal. Case 9 showed exudate in the cribriform plate, but the nasal cavities were free. In the cases with exudate at the base, the sheaths of the fifth nerve, the Gasserian ganglia, and the tissues about the pituitary body sometimes showed frank pus.

The other organs offered some things of note. Thus, all cases, except the otitic cases (9 and 12) (in Case 12 the examination was limited to the head), showed acute lesions in the lungs, lobar pneumonia in Cases 2, 5 (organizing), 7 and 8; bronchopneumonia in Cases 1 and 10; edema and congestion in Cases 3, 6 and 9; encysted pleurisy in Case 4. These lung lesions were probably responsible for the origin of some brain infections. The same doubtful correlation occurred in our series of brain infections with *Staphylococcus pyogenes aureus,* in which focal pulmonary lesions were either grossly prominent or made out microscopically in all six cases.

Aside from the lungs, the organs of the trunk showed little. Case 5 was a case of malignant endocarditis (aortic). Case 4 showed, in addition to encysted pleurisy, an acute pericarditis.

Chronic lesions, which might possibly have a bearing on infection, were found in a few cases. Half the cases (1, 3 (marked), 6, 7, 8 and 10) showed arteriosclerosis; and, of these, Case 6 showed a hypertrophied, dilated and fatty heart. Case 4 showed chronic nephritis, Case 8 chronic adhesive pericarditis, Case 10 cirrhosis of the liver.

GENERAL SUMMARY OF MICROSCOPIC FINDINGS.

Alterations were found in several of the tissues, particularly in the meningeal connective tissue, the walls of the arteries and to some extent of the veins, and in the nerve tissue, under which may be considered the reaction of the subpial neuroglia and the immigration of polynuclear leucocytes.

The meningeal tissues contained numerous cells, chiefly polynuclear leucocytes and mononuclear elements in varying proportions. In Cases 3, 6, 8, 10 and in parts of Case 11 the polynuclear leucocytes plainly outnumbered the mononuclear cells. In Cases 1, 4, 7, 12 and in parts of Cases 5 and 11 there are more mononuclear cells. Cases 2 and 9 showed these cells in about equal numbers.

Phagocytosis of mononuclear cells for polynuclear leucocytes was best marked in Cases 1, 4, 5, 9, 11 and 12, in most of which cases the mononuclear cells outnumbered the polynuclear cells. Phagocytosis for bacteria was best marked in Cases 1 and 2 (the two cases of almost pure encephalitis).

The general distribution of the meningeal exudate was fairly constant. Certain central spaces in the pia mater were likely to contain masses of polynuclear leucocytes even in cases in which the perivascular tissues and the tissues at large were filled with mononuclear cells. Another characteristic was the distribution of the fibrin, which was found in abundance about the veins and in that part of the pia mater just overlying the nerve tissue. There was no evidence of focal necroses in the exudate, although portions of the exudate stained poorly in Cases 7 and 11.

The arteries of the meninges showed lesions in all the meningitic cases, but these lesions were not characteristic in Cases 1 and 2. The intima was lifted or dissected away from the elastica by an accumulation of cells, largely polynuclear leucocytes. All degrees of this process occurred up to occlusion of the lumen. The lesion was frequent and marked in Cases 3, 7, 8, 10, 11 and 12, less frequent in Case 4 (in which the arteries of the spinal pia mater were affected), and in Cases 5, 6 and 9.

Somewhat less common but more striking were the lesions in the veins (Cases 5, 6, 7, 8, 12 and in some other cases to a minor degree). The walls of the larger veins, especially the large sulcal veins, showed the process more distinctly than the venules. In the walls of the venules there was occasionally a thorough infiltration with polynuclear leucocytes and minor proliferative changes; but in the larger veins there was a prominent overgrowth of lining cells, among which the polynuclear leucocytes lay in a variety of ameboid shapes.

Case 6 was distinguished by the presence in the walls of numerous minute mural organizing thrombi (ten, for example, crosscut in a section of a vein about 1 mm. in diameter). Case 12 (a case of sinus thrombosis) showed occlusion of small veins of the pia mater also.

The reaction of the nerve tissue to the infection may be considered under the head of vessels, neuroglia and nerve cells with their adnexa.

The vessels of the cortex showed adventitial infiltration with polynuclear leucocytes in various degrees. Case 1 showed great accumulations of phagocytic cells about some vessels. The nerve cells failed to show notable or any rate constant changes.

The neuroglia exhibited, in many cases, a tendency to cell increase in the subpial layer. Three cases (6, 9 and

11) showed numerous mitoses. Case 6 showed mitoses among cells regarded as satellite cells. Cases 1, 3, 4 and 5 also showed cell changes in the neuroglia, eccentrically swollen cell bodies, multiple nuclei, or fibrils in apposition to cell processes. In Cases 2, 7, 8, 10 and 12 neuroglia changes were few or absent. In Case 2 (fulminant case in a boy of 10) the original layer of neuroglia was thin and the involvement of the meninges slight. In the other cases which showed no acute neuroglia change the original subpial layer happened, as a rule, to be dense. This character of the original neuroglia, however, can scarcely govern the occurrence of acute changes, since Cases 3 and 6 had dense subpial neuroglia, but marked acute changes.

The cortex was penetrated by polynuclear leucocytes in most cases. This penetration was free in Cases 2, 4, 5, 9 and 12. Occasional or fairly frequent examples of leucocytes in the substance were found in all the other cases, except 7, wherein very few examples occurred.

EXPERIMENTAL MATERIAL.

Inoculations were made in guinea-pigs with different strains of the pneumococcus kindly supplied us by Drs. C. W. Duval and P. A. Lewis in the course of their pneumococcus work in 1905.[3] The results of inoculation with the various strains (sixteen), as tested by the appearances in guinea-pigs killed four days after inoculation, were various, ranging from negative to pronounced suppuration. Work was pursued with a single organism only (C D 6 of the series isolated by Duval and Lewis). The same method, in general, was employed as in our work with *Staphylococcus pyogenes aureus,* the method of simultaneous inoculation of several animals and histologic examination of animals killed on successive days during the course of the disease.

As in the work with *Staphylococcus pyogenes aureus,* various methods of inoculation were employed. The intrapulmonary method, applicable in staphylococcus work, is not well suited to pneumococcus work in the guinea-pig. Subdural inoculations are effective, but are open to the usual objections that the destruction and hemorrhage produced by the operation obscure the results of infection.

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[3] Studies on the Pneumococcus, C. W. Duval and P. A. Lewis, Jour. of Exp. Med., August, 1905.

Resort was had, therefore, to a method of inoculation by way of the orbit. The syringe needle is introduced at the line of reflection of the conjunctiva on the temporal side of the globus oculi. The bouillon culture is then slowly introduced into the tissues of the orbit. Exophthalmos follows, but subsides in a few minutes. There is occasionally transient circular progression toward the side of inoculation. This method may be modified by plunging the needle through the wall of the orbit into the brain. Since the conjunctiva, as a rule, is free from bacteria, the method of orbital inoculation effects entrance into the interior of the cranium more advantageously than other methods. This method is said to have been first used in rabies work. Other methods, as nasal and ear-plate inoculations, were used, but are not so good for general work as the orbital method.

We found difficulty in recovering the pneumococcus from the organs of the inoculated guinea-pigs and were unable to obtain a complete single series of daily stages of the brain lesion with positive cultures in all. It would be possible, doubtless, to obtain an unbroken series of positive cultures by using very numerous animals and the rabbit's blood agar culture medium employed by Duval and Lewis in their investigation. Positive results, however, were obtained in a sufficient number of brain cultures in the series with organism C D 6 (Series of Duval and Lewis).

The general result of the experimental work is as follows:

Of the four-day orbital inoculations, seven cultures gave slight or negative results; three cultures gave accumulation of chiefly mononuclear cells in the meninges; two cultures gave very slight exudation with congested veins filled or lined with polynuclear leucocytes; three cultures gave exudates (recalling many of the human exudates) with polynuclear leucocytes and mononuclear cells in various, about equal proportions; one culture gave polynucleosis.

A series of brains from guinea-pigs inoculated in the orbit with organism C D 6 showed the following:

Six hours after inoculation many veins showed leucocytes arranged as in the inert layer. The tissues about the base and cerebellum showed a light exudation of polynuclear leucocytes and considerable hemorrhage. In the exudate were occasional polynuclear leucocytes with deeply eosinophile granulations. The third ventricle showed hemorrhage with occasional polynuclear leucocytes; the mural ependyma showed no changes. The brain substance was normal, except for a few shrunken and metachromatic nerve cells; there was no penetration of substance by polynuclear leucocytes.

The brains after one, two and three days would in many cases be difficult to pick out and arrange in series, on account of variations in the amount of exudate and hemorrhage. More and more cells of the mononuclear series entered; but it was hard to estimate these when far outnumbered by polynuclear leucocytes and to distinguish them from such cells normally present. In one brain, two days after inoculation, a few minute hemorrhagic abscesses were found.

The condition four days after inoculation is described more fully, since four-day material can be recommended for test work. Four days after inoculation the tissues between the laminæ of the cerebellum and at the base are distended with a heavy exudate in which polynuclear leucocytes somewhat outnumber the mononuclear cells. Fresh hemorrhages in the pial meshes are few and small. An occasional phagocyte containing polynuclear leucocytes occurs in the adventitia of veins. Cells of the lymphocyte series occur, with now and then a plasma cell; but these cells occur in foci, whereas the polynuclear leucocytes and the mononuclear cells having vesicular nuclei are of general distribution. The ventricles show slight hemorrhage, a light exudate of polynuclear leucocytes and occasional phagocytes containing polynuclear leucocytes. Penetration of the cortex by polynuclear leucocytes is frequent and is particularly free in the cerebellum, where leucocytes are found deep among the cells of the granular layer.

A comparison of the four-day material after subdural injection of equal amounts of the same culture shows that the subdural lesions are of more advanced character, in the sense that polynuclear leucocytes are fewer, pigment-containing cells more numerous, and karyokinetic figures in the adventitial tissues more frequent than in the orbital material.

The exudates, however, are in somewhat different loci, the exudate after orbital inoculation is largely basal after subdural inoculation over the convexity.

The pictures on succeeding days are only roughly open to serial arrangement from internal evidence. The ependymitis, not so marked as in our series with *Staphylococcus aureus,* plays a minor part. There is rarely any destructive encephalitis. We have, therefore, only the meningeal picture, which as a single guide is unsatisfactory.

In from two to five weeks there was no longer evidence of disease in our series, except a multiplication of glia cells along the meninges and beneath the ependyma. The latter we are as yet unwilling to ascribe to the effects of the pneumococcus, since in many guinea-pigs the process is found from other causes. Mitoses beneath the ependyma are occasionally seen at various points in the series.

GENERAL SUMMARY AND REMARKS.

The foregoing is a report of cases grouped together as showing effects of pneumococcus brain infection. The clinical and anatomic varieties which they exhibit are only in part explained on present evidence. A long series of cases with parallel differential work on the best bacteriologic lines will be required to settle questions brought up by the various extent and effect of lesions like arteritis and phlebitis, by the varying prominence of polynucleosis and mononucleosis in the meningeal exudate, by variation in the phagocytic properties of the cells involved, and by the varying extent and character of the attendant cellular gliosis.

Clinically viewed, these cases are quite ill assorted. The group includes fulminant and wholly obscure cases, cases not to be told from severe pneumonia, clearly otitic cases, septicemic phenomena, and cases a week old or longer which are clearly cerebral or meningitic in character.

Anatomically viewed, the pneumococcus produces in the meninges and brain substance of man a type of inflammation in which cellular exudation and fibrin formation are prominent.

The picture postmortem varies from focal or diffuse red softening to purulent leptomeningitis and ependymitis and occasionally abscess formation. The meningeal exudate is almost constant on the convexity. The base is frequently involved and, with the base, often also the ventricles and the cord.

The histologic picture is more various than the anatomic picture. The meninges contain a cellular exudate which varies in the proportion of polynuclear leucocytes and mononuclear cells. Phagocytosis on the part of mononuclear cells for polynuclear leucocytes is best marked in cases in which the mononuclear cells outnumber the polynuclear leucocytes. The meninges in individual cases are fairly constant in the cell proportions found. Fibrin is found about the veins and adjacent to the nerve tissue.

The arteries characteristically show lifting of the endothelium by cellular exudate. The veins often show proliferative changes in the intima with infiltration by polynuclear leucocytes (characteristic in large sulcal veins). Two cases showed mural thrombus formation in the veins.

Seven cases out of twelve showed increase or other signs of change in the neuroglia, especially of the subpial layer.

Penetration of the cortical tissue by polynuclear leucocytes is almost constant.

Orbital inoculations in the guinea-pig showed remarkable variety in the results with different cultures. With the cultures yielding positive results, a general but not constant tendency is to the production of exudates with a high proportion of mononuclear cells of the phagocytic series. A series of orbital inoculations with culture identical throughout exhibited clearly the same tendency. The exudation of polynuclear leucocytes is primary, however, and may be noted in six hours. The exudate is at its height in three, four or five days and leaves no trace in from two to five weeks. Ependymitis and encephalitis are not prominent. The guinea-pig inoculations, as a rule, produce no clinical sign.

Cerebral Seizures with Suboccipital Pain: Miliary Cerebral and Gross Vertebral Aneurysms

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Reprinted from the Boston Medical and Surgical Journal
Vol. cliv, No. 12, pp. 312–314, March 22, 1906

BOSTON
THE OLD CORNER BOOK STORE
(INCORPORATED)
27 AND 29 BROMFIELD STREET
1906

CEREBRAL SEIZURES WITH SUBOCCIPITAL PAIN: MILIARY CEREBRAL AND GROSS VERTEBRAL ANEURYSMS.*

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From the Pathological Laboratory of the Boston City Hospital.

THE following case suggests the difficulty of diagnosis in cranial conditions anatomically simple. A woman of sixty-nine years presented a series of cerebral seizures without focal signs, leading to fatal issue in nineteen days. The seizures were ushered in by boring suboccipital pain. The autopsy revealed several successive voluminous hemorrhages so situated in various parts of the cerebrum that the fibres of the projection system were largely spared. The small cerebral arteries, both of the cortical and the ganglionic systems, were beset with miliary aneurysms. Both vertebral arteries opposite the junction of bulb and cord, showed gross aneurysmal dilatation.

I. *Clinical History.* — Widow of sixty-nine years. For a year before her last illness she showed a tendency to drowsiness in the daytime and would even fall asleep in company.

She was taken one evening, nineteen days before her death, with sudden, severe, suboccipital pain, described as boring and confined to a spot the size of a fifty-cent piece. The pain was at first attributed to neck strain, produced by gazing up at mural paintings the afternoon of the attack. The pain was followed shortly by projectile vomiting with retching. These symptoms persisted for two days. The day after the attack the pain became less severe and changed to a dull ache, constant in the original situation and varying in intensity, without, however, relation to movement or position of the head and neck. On the fourth and fifth days of the illness there were slight chills with sweating. Evening rise of temperature from 1° to 3° F.

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* Read Feb. 15, 1905, at a meeting of the Boston Society of Psychiatry and Neurology.

Examined Nov. 1, 1905 (W. D. R.). Development good. Considerable adipose tissue. Mind clear. Attitude cheerful. Eyes: Movements normal; pupils react readily to light and distance. Head: No tender spots; no bruit heard; no rigidity or retraction of neck; no inequality in sides of face; no paralysis of facial muscles. Tongue: Protruded straight, dry, coated, cleaning in center. Breath foul. Throat: Negative. Pulses: Regular, 68, of good volume with increased tension. Moderate degree of radial and brachial arteriosclerosis. Heart: Right border two finger breadths to right of right edge of sternum; upper border at third rib; left border in nipple line; apex in fifth space in nipple line; action regular; sounds of good intensity; systolic blowing murmur over aortic orifice; aortic second sound accentuated. Lungs: Negative, except for a few moist râles in both bases behind. Abdomen: Negative. Spleen: Not felt. Extremities: Normal. Reflexes: Superficial reflexes slow; knee jerks slow and equal; Kernig's sign absent; Babinski's sign absent. Leucocytes, 17,000.

The evening of Nov. 2 (eighth day of illness) came another attack of boring pain, localized as before, lasting eight or ten minutes. The mind wandered during the attack. There was steady improvement. The temperature remained slightly elevated. The pulse ranged from 60 to 68. The mind was clear. The attitude cheerful. The dull aching pain continued in the back of the head.

The morning of Nov. 13, after passing a comfortable night, the patient complained of a sudden cold feeling in the forehead. Consciousness became clouded. Coma and Cheyne-Stokes breathing set in with death in about two hours.

Clinical Summary. — Woman of sixty-nine, with moderate arteriosclerosis and an enlarged heart. Attacks of severe, boring pain, localized in an area the size of a fifty-cent piece, in the suboccipital region (first and eighth days). Slight chills (fourth and fifth days). Temperature slightly elevated with morning remissions. Leucocytes, 17,000. Death in coma two hours after a sudden cold feeling in the forehead (nineteenth day).

II. *Autopsy Findings* (E. E. S.) — Well developed woman of middle height. Nutrition good. No edema. Pupils equal, not dilated.

Trunk: Subcutaneous fat of abdomen 5 cm. deep; cavities normal; mesentery very fatty; mesenteric lymph nodes not palpable.

Heart: Considerable epicardial fat; heart much enlarged; valves normal, except for raised yellow areas of sclerosis in mitral leaflet; muscle of both ventricles unusually firm and without opacities; right ventricle 1 cm., left ventricle, 2.5 cm. thick; chambers contain freshly clotted and liquid blood; coronary arteries show nodular sclerosis. Lungs: Normal; post-mortem congestion of bases beginning; slight superficial fibrous thickenings at each apex; bronchial lymph nodes not remarkable. Spleen: 18 cm. long; capsule smooth and slightly thicker than usual; substance firm, not pulpy; Malpighian bodies made out; trabeculæ slightly increased; splenic artery shows marked stiffening. Liver: Chestnut brown, firm; lobulation made out with difficulty. Gall bladder: Small, buried in smooth old adhesions; contains no stones. Pancreas: Normal. Gastro-intestinal tract: Normal on inspection and palpation. Kidneys: Strip readily, leaving a roughened surface; numerous small cysts over anterior surfaces of both kidneys; pea-sized aberrant adrenal, 2 cm. from hilum, midway between poles imbedded in anterior surface of right kidney; substance shows opacities suggesting fat. Pelves normal. Adrenals normal. Genitalia: Atrophic.

Head: Hair fairly thick and streaked with gray. Scalp: Strips readily. Calvarium: Thick (in places 1 cm.) and dense. Dura: Tightly adherent to calvarium over all, but inseparably adherent to occipital bone. Sinuses: Normal. Arachnoidal villi: Slightly developed. Pia mater: Everywhere reddened by hemorrhage or dissolved blood pigment. The frank areas of hemorrhage involve the sulci of the anterior and mesial surfaces of the cortex cerebri in the area of distribution of the anterior cerebral arteries. The flanks and posterior pole of the brain show reddening, and congestion of superficial sulcal veins, but no fine injection. Over the sulcal veins of the vertex are slender streaks of fibrous thickening. Vessels: At base show diffuse and nodular sclerosis. Both vertebral arteries show fusiform aneurysmal dilatations, 0.75 cm. in diameter. The circle of Willis is apparently pervious. The primary branches of the middle cerebral arteries show nodular sclerosis in patches 0.5 to 1 cm. long.

Substance. — Convolutions flattened. Anterior pole of left hemisphere contains a core of clotted blood and tissue detritus occupying the centrum semiovale under the first and second frontal gyri. The clot is fresh and can be readily turned out from its bed above the forceps minor. The upper fibers of the forceps minor and anterior quarter of the tapetum have been destroyed by the hemorrhage and show a moist, ragged, grayish surface. The hemorrhage approaches the surface in the gyrus rectus and about the olfactory lobes; thence the blood has oozed into the orbital and polar sulci.

A similar hemorrhage fills the white matter of the right anterior pole above the forceps minor, but has broken down the gray matter at the pole. The clots on the right side cannot be turned out so readily as those on the left. Small vessels with tightly adherent small masses of mixed gray and red clot are demonstrable in the bed of the hemorrhagic area. Fresh oozing into the cortical sulci has occurred on the right side as on the left. The ventricles contain no blood and no increase of fluid. Ependyma normal. Posterior parts of lateral choroid plexuses cystic. Basal ganglia, inter-brain, isthmus, cerebellum normal.

Pituitary surrounded by effused blood.

Blood serum cultures from hemorrhage into right frontal lobe and from right basal ganglion remained sterile.

The pia mater and vessels were macerated out in running water by Mr. J. B. Ayer, and both the cortical and the ganglionic systems of arteries proved to show in their smaller branches numerous miliary aneurysms. These were sometimes saccular, sometimes fusiform in shape.

Anatomical Summary. — General arteriosclerosis (aortic, coronary, cerebral, splenic, renal). Fusiform aneurysms of both vertebral arteries. Miliary aneurysms of cortical and ganglionic arterial systems.

Extensive multiple cerebral hemorrhages (of varying age) in substance of anterior poles of brain and elsewhere, with oozing into superficial pia mater.

Hypertrophy of heart, endocardial sclerosis, arteriosclerotic nephritis, apical scars of lungs, chronic pericholecystitis, chronic adhesive external pachymeningitis, chronic fibrous leptomeningitis, aberrant adrenal in right kidney.

III. *Microscopic Findings.*— The microscopic examination was chiefly confirmatory of the gross findings. The organs of the trunk showed relatively more arteriosclerosis than the intracranial tissues. The kidney showed numerous advanced chronic changes with extensive arteriosclerosis, numerous atrophied glomeruli and tube-casts. The lungs showed no signs of acute inflammation. The spleen showed numerous hemorrhages into the pulp and a heavier framework than usual, but failed to show acute alterations.

Numerous sections were made from the cerebrum, medulla and cord. The cerebral hemorrhages proved to be distinguishable into fresh hemorrhages, hemorrhages with numerous phagocytes containing unaltered blood globules, and hemorrhages containing pigment-phagocytes. Of the fresh hemorrhages, many were small dissecting hemorrhages about the smallest vessels; but very few of these vessels showed demonstrable ectasia or alteration in the elastica. The older areas exhibited numerous phagocytic cells inclosing blood globules, sometimes in scores. The most numerous phagocytes occur in the sulci in the neighborhood of the larger vessels. The pigment-phagocytes are generally distributed and have often lost their spherical shape. There are strikingly few signs of cellular exudation anywhere in the meninges, although an occasional large sulcal vein will show a minute collection of cells of the lymphocyte series at a single focus in the adventitia. Signs of reaction on the part of the nerve tissue are few. There is an occasional strip of the outer cortical layer, which shows a number of swollen neuroglia cells; but these are enmeshed among rather dense fibrils, and there is evidence of a general but focally varying superficial fibrillar gliosis, probably long antedating the hemorrhages and still condensing. The pyramidal nerve cells show considerable over-pigmentation.

Similarly in the region of the vertebral aneurysms the diffuse gliotic alteration of the superficial zone and in the neighborhood of the posterior roots is part and parcel of a more general process, exhibited equally in the medulla beyond the zone of immediate aneurysmal pressure. Nevertheless, we cannot exclude this gliosis from influencing in some degree the regionary pain. The vessels of the cord and medulla themselves show little alteration. There was no convincing evidence of alteration in the nerve bundles in the walls of the vertebral aneurysms. Slender collections of cells of the lymphocyte series lie in the connective tissues opposite the middle of the walls of the aneurysms, where breaks in the elastica and thinning out with occasional fenestration of the muscular layer occur.

IV. *Remarks.* — Aneurysms of the vertebral arteries, like those of the other cerebral arteries, are rarely made out in life and are usually discovered by medical examiners in cases of sudden death. v. Hofmann, 1894, mentions ten cases of aneurysm of vertebral artery with fatal rupture, over against twenty cases of Sylvian, thirteen cases of carotid, and ten cases of basilar aneurysm in the same series.[1] Curiously enough, the youngest victims of basal aneurysm in v. Hofmann's series showed left vertebral aneurysm (a girl of ten dying suddenly in convulsions, and a boy of fourteen dying suddenly). From time to time, however, cases of vertebral aneurysm without rupture and with definite symptoms have been reported. As examples of these and for comparison with our own case, we have abstracted in particular the irritative case of F. Schultze, 1875, the slowly destructive case of Ladame and Monakow, 1900, and the case with fatal rupture of Rindfleisch, 1905.

F. Schultze, 1875, reported a case of aneurysm the size of a cherry in the left vertebral artery about one-half inch from the junction with the basilar artery, so placed as to compress the left seventh and eighth nerve roots.[2] The subject was fifty-six years old and died of phthisis, showing no effects of the aneurysm save a pronounced *tic convulsif*. The tic had lasted about a year, and consisted in brief, rapidly recurring clonic contractions of the left side of the face, starting up or augmenting with speech or mastication. The intervals without tic varied. The frontalis, ear muscles and palate were not involved. Pain was absent. There were no points of pressure by which to evoke the contractions.

Ladame and Monakow, 1900, reported a case of aneurysm of the left vertebral artery in a man of sixty-eight, with a history of syphilitic infection at thirty.[3] The symptoms began about two years before death with vertigo and attacks of angina pectoris. After a particularly violent apoplectiform attack, a cerebellar gait developed, with dysarthria, some dyspnea, cerebellar agraphia, and occasional pains in the left arm. After six months of such symptoms, the patient had a violent seizure with vertigo and vomiting but without loss of consciousness. Thenceforward the patient always fell to the left, would no longer walk, stand or sit up, and showed loss of pain and temperature sense on the right side of the body, left abducens palsy, slight left ptosis, and narrowed left pupil. Swallowing became difficult, stupor and coma followed, with death two years after onset of earliest symptoms, forty days after the last seizure. The autopsy showed an aneurysm the size of a pigeon's egg of the left vertebral artery near its junction with the basilar artery. There was corresponding atrophy of the pons, cerebellum, olive, pyramid, and left acoustic nerve, with slight atrophy of the left fifth, sixth, ninth and tenth nerves.

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[1] v. Hofmann: Ueber Aneurysmen der Basalarterien und deren Ruptur als Ursache des plötzlichen Todes. Wiener Klinische Wochenschr., November, 1894.

[2] F. Schultze: Linksseitiger Facialiskrampf in Folge eines Aneurysma der arteria vertebralis sinistra. Virchow's Archiv., Bd. 65, H. 3, 1875.

Rindfleisch, 1905, reports a case of aneurysm of the right vertebral artery, with fatal rupture, in a woman of fifty-one.[4] For ten years she had had attacks of asthma and edema of the legs. For three years she had had eructations and headaches. Three days before entrance to the hospital she had been taken with sudden eructations and pains in the back of the head. On the day of admission she had two attacks of stupor with facial cyanosis, transient Cheyne-Stokes breathing, and râles in the lungs. The first attack began with a feeling of terror and screams. In both attacks the corneal and patellar reflexes were lost. The pupils were narrow and reacted to light.

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[3] Ladame et Monakow: Aneurysme de l'artère vertebrale gauche. Nouvelle Iconographie de la Salpetrière, Tom xiii, 1900.

[4] Rindfleisch: Zur Kenntnis der Aneurysmen der basalen Hirnarterien und der bei den intrameningealen Apoplexien auftretenden Veränderungen der Cerebrospinalflüssigkeit. Lichtheim's Festschrift. Deutsches Archiv f. klin. Medizin, Bd. 86, Heft 1–3, 1905.

On admission were noted subfebrile temperature, slight edema of the legs, moderate facial cyanosis, diffuse râles in the lungs, weak skin reflexes and weak normal plantar reflex, absent abdominal, patellar and Achilles reflexes and hemorrhages in the fundi. Coma set in shortly, with slowed pulse, increased cyanosis and deep, noisy breathing. The patient improved with artificial respiration, but remained drowsy. Lumbar puncture yielded fluid containing considerable blood, which failed to clot. Death followed on the third day after admission to the hospital in coma, with cyanosis and cessation of breathing while the heart remained beating.

The autopsy showed all the fossæ at the base of the brain filled with blood. The clots overlay the medulla oblongata, pons and chiasma. The blood was derived from the rupture of a bean-sized aneurysm situated on the mesial side of the right vertebral artery about 0.5 cm. before the junction of the two vertebral arteries.

The earlier literature of vertebral aneurysms is given by Lebert, 1866.[5] No case like the present appears to have been recorded, although Gray's "Anatomy," under the heading of "Surgical Anatomy of the Vertebral Arteries," refers to a case of Drs. Ramskill and Bright, in which regionary pain was due to disease of this artery.

Our own case may be classified as irritative. It is probable that the striking attacks of suboccipital pain were brought on by a combination of factors, through pressure of the vertebral aneurysms, aided by heightened intracranial pressure attending the cerebral hemorrhages. The chronic alterations of the cord and posterior root areas were no more marked than the chronic alterations above and below the region of the vertebral aneurysms; yet it is possible that the spinal gliosis found may be related in some way with the attacks. Attention may also be called to the dense pachymeningitis of the posterior cranial fossa. A closer study of non-destructive lesions would be desirable in such cases.

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[5] Lebert: Berliner klin. Wochenschr., 1866.

Pain in the back of the neck (*regio nuchæ* of His) is a symptom of some interest. Over and above a number of obvious causes, such as local inflammation of the skin, the muscles and the supportive tissues, cervical caries and osteomyelitis, pachymeningitis, leptomeningitis, neoplasms and various agents of local compression of peripheral nerves of the upper cervical segments, there are a number of obscure conditions of nuchal pain and particularly of pain in the middle of this region (*fovea nuchæ* of His). Special names are often reserved for the fixed or relatively permanent neuralgia of this region, as cervico-occipital neuralgia, occipitodynia. Occipitodynia in a certain context of symptoms is accepted as a sign of neurasthenia. Occipitodynia figures prominently in the well-known diagrams of referred pain in visceral disturbance, often under the caption "spinal irritation."

The search for the particular cause of a given pain is not always as minute as it might be. Pains are, perhaps, too readily classed as functional. The orthopedists occasionally insist on the possible relation of neuralgia to the pressure of dilated or varicose veins upon the regionary nerves. The present case brings out the possibility that arterial disease may effect the same result in one of the favorite sites for functional pain.

The puzzling features of this case of cerebral seizures with coma, ushered in by suboccipital pain, appear to be reasonably accounted for by the post-mortem findings: numerous successive hemorrhages into the silent areas of a cerebrum showing numerous miliary aneurysms, and gross aneurysms of both vertebral arteries opposite the junction of bulb and cord.

A CASE OF GLIOMA OF THE FRONTAL LOBE WITH INVASION OF THE OPPOSITE HEMISPHERE.

By E. E. SOUTHARD, M. D.,

Instructor in Neuropathology and Charles Eliot Ware Fellow, Harvard University Medical School; Pathologist to the Danvers Insane Hospital; Second Assistant Visiting Pathologist, Boston City Hospital.

(From the Pathological Laboratory of the Danvers Insane Hospital.)

Reprinted from
AMERICAN JOURNAL OF INSANITY
Vol. LXII, No. 4, April, 1906

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(*From the Pathological Laboratory of the Danvers Insane Hospital.*)

The following case of glioma of the frontal region led to death after symptoms lasting ten weeks. The autopsy showed discrete nodules of neuroglia tissue in the cortex of the right frontal lobe, together with extensive confluent areas of softening in the medullary center beneath. One of the nodules had invaded the opposite hemisphere.

From the gross appearances the question might arise whether the new growth did not originate in several centers. The microscopic examination showed identity of structure both in the nodules and in the tissue of the medullary center, with apparent differences due to necrosis of parts of the tumor. The tumor is best taken as monocentral, and the apparently discrete nodules are best interpreted as processes of a single tumor, necrotic in the middle and varying in rate of growth along different radii.

In examining the tissues at the line of contact between the tumor and the invaded pia mater, the methods recently advised by Mallory[1] have proved indispensable.

I. Clinical History.

F. F., born in Belgium, a mill-worker of forty-one years, was committed to the Danvers Insane Hospital, September 6, 1904. Onset, two months before commitment, with continual headache and general lassitude. Later he began to vomit after meals without nausea and became subject to incontinence of urine and feces. Mental symptoms developed at the same time: dulness, loss of memory, disorientation for time, depression. A week before commitment he had been arrested as drunk.

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[1] F. B. Mallory, A Contribution to the Classification of Tumors. Journ. Med. Research, XIII, 2, January, 1905.

He was too weak to walk alone on admission and showed a coarse tremor of hands and a slight tremor of tongue. The patellar, achilles, triceps, and wrist reflexes were exaggerated. Babinski sign absent. Pupils reacted to light, also consensually. Sensation good as far as tested. Motor restlessness during examination: with eyes closed, turned head from side to side frequently; drummed with fingers on side of bed. Was got to count correctly to twenty. In saying alphabet, repeated only a few letters. On being asked leading questions, was got to say he heard voices; but nothing more definite in respect to hallucinations was elicited. The urine contained casts and a large trace of albumin.

He lay in bed a week without change, dull, weak, occasionally untidy. Then came a rather sudden change. Restlessness and continual changes of posture of limbs set in, without well-defined convulsion. Next morning (nine days after entrance) deep stupor had developed, with relaxation of extremities, non-reaction to pain, head turned to right, right external strabismus, right pupil larger than left, non-reaction of pupils to light, knee-jerks equal and moderate, and sharp upward contraction of great toe in both feet on stroking soles. Death the next morning.

I am indebted for these notes to Dr. H. M. Swift, assistant physician to the Danvers Insane Hospital.

Clinical Summary.

Belgian mill-worker of forty-one years. Headache, vomiting, incontinence, lassitude, dulness, memory-disturbance, depression, two months before commitment. Once arrested as drunk. Dulness, weakness, tremors of hands and tongue, exaggerated knee-jerks and arm-reflexes. Eight days after commitment, restlessness set in, followed next day by stupor, deviation of head to right and right external strabismus, dilatation of right pupil, and Babinski sign on both sides. Death ten days after commitment, about ten weeks after onset of symptoms.

II. Anatomical Findings.

Following are the findings in the head with a summary of findings in the trunk. Autopsy four hours after death.

Head.—Scalp not notable. Diploëtic spaces of calvarium in temporal regions show congestion. Inner surface of calvarium moist. Dura non-adherent, tense; bulging in temporal regions. Sinuses contain thin red clot. Inner surface of dura dry. Falx adherent to pia mater over rostrum.

Pia Mater dull, nowhere thickened or hazy. Contiguous surfaces of frontal lobes under falx are lightly adherent.

Vessels.—Veins of pia congested. Arteries normal, except 7 mm. of the basilar artery at the vertebral end, which is pale and hard.

Substance.—Convolutions of convexity flattened. Focal lesions are visible in the right hemisphere in three places: the right rostral convolution, the tip of the right frontal lobe, and the inner margin of the right frontal lobe midway between the tip of the lobe and the anterior central convolution. (See text figures 1 and 2.)

The lesion in the right rostral convolution is a somewhat firm mass about the size of a hickory nut, which bulges across the longitudinal fissure to be received in a depression 1 cm. deep in the opposite hemisphere. The outer surface of the mass is darker than the adjacent cortex and dotted with opaque yellowish-gray flecks. Section shows a reddish-gray surface with numerous vascular points and areas of hemorrhage besides opaque yellowish-gray streaks of homogeneous soft material. The lesion is surrounded externally by a thin shell of altered cortical substance and internally by an opaque yellowish-gray stripe 3-4 mm. wide.

The lesion of the tip of the right frontal lobe is separated from the rostral lesion by an interval without gross change, but is similar in appearance to the first. The adjacent cortical surface is puckered and of increased consistence.

The third focal lesion is quite distinct from the two others but a little smaller, and superficially recalls the appearance of a septic infarct. The area is rather sharply circumscribed, and its surface is slightly raised, finely roughened, reddish, and dotted as if with small abscesses. There is, however, no surrounding zone of

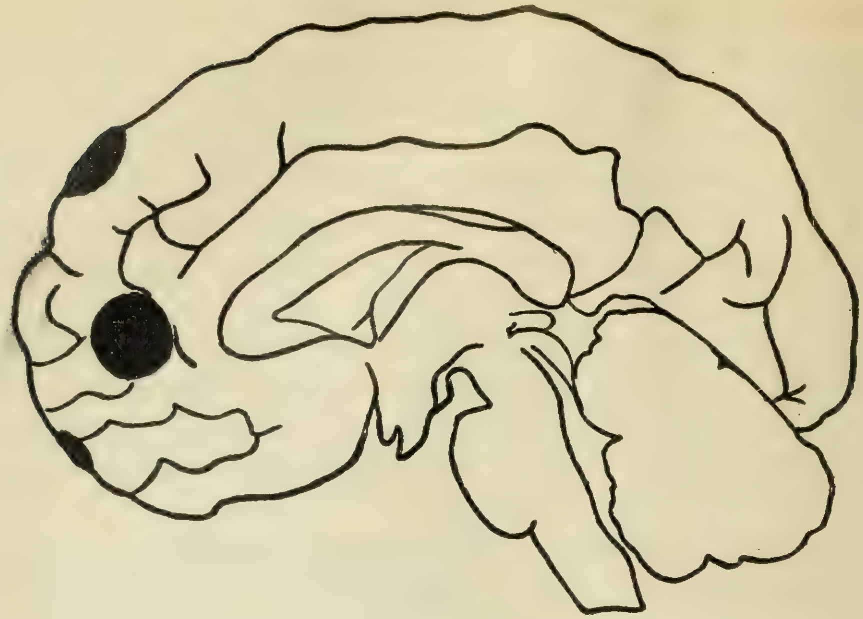


FIG. 1.—(Dalton, 1885, Plate A, vi.) Mass in right rostral convolution, with two other masses as shown on median aspect.

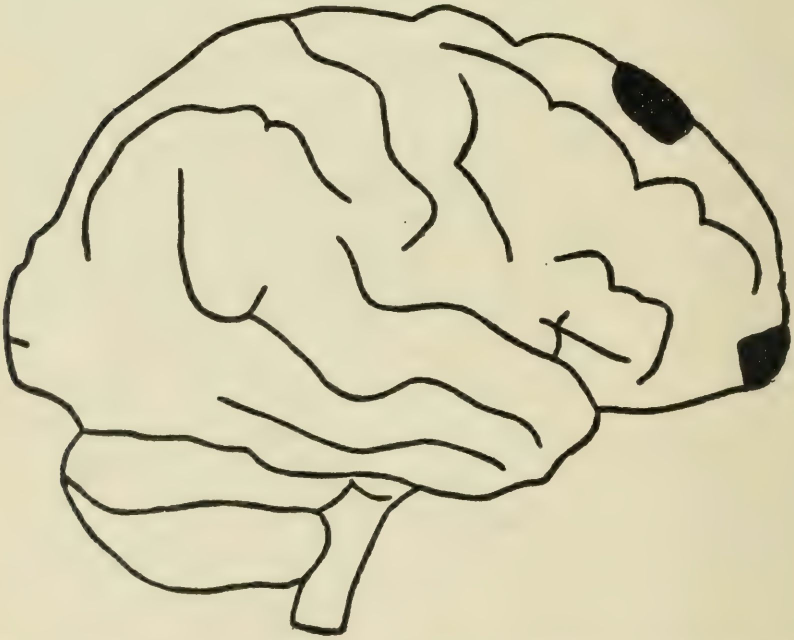


FIG. 2.—(Dalton, Plate A, ii.) Masses on outer aspect of frontal lobe.

hyperemia. The section surface is similar to those of the other focal lesions.

The centrum semiovale in the right frontal region is soft and full of hemorrhages as far back as a plane about 3 mm. posterior to the tip of the caudate nucleus. In the middle of this hemorrhagic area is a homogeneous grayish-brown semi-fluid material. The remainder of the centrum semiovale of the right hemisphere is edematous.

The left hemisphere shows no focal lesion except the depression into which fits the lesion of the right rostral convolution. The tissues lining the depression and the surrounding convolutions are puckered and cartilage-like. The white matter beneath the depression is hyperemic.

The autopsy was performed by Dr. A. M. Barrett, to whom I am indebted for the material.

Anatomical Summary.

Three discrete lesions of right frontal lobe. Hemorrhage and edema of right centrum semiovale in frontal region. Chronic focal leptomeningitis. Congestion of pial veins. Chronic diffuse nephritis. Slight bilateral bronchopneumonia. Anomaly in origin of mesentery.

III. Microscopic Findings.

The organs of the *trunk* show little of interest. The *heart muscle* shows central brown pigmentation of a small proportion of fibers. Portions of the *lung* show congestion and an even cellular exudate with little fibrin, masses of many kinds of bacteria, chiefly lanceolate diplococci, many of the latter enclosed in polynuclear leucocytes. The bronchial mucosa is usually well preserved, but the lumen may contain poorly staining tissue fragments loaded with bacteria. The *spleen* shows a surplus of trabeculæ, an increase of reticulum, hyaline changes in the walls of Malpighian arterioles, areas of phagocytic cells in center of a few Malpighian bodies, pigment-phagocytes and numerous polynuclear leucocytes in the pulp spaces. Many of the central *liver* columns show pigmentation. The *kidney* shows overgrowth of fibrous tissue in the pyramids, thickening of the capsule of some glomeruli, homogeneous casts chiefly in straight tubules, and thickening of intima in arteries in intermediate zone. *Pancreas* and *adrenal* negative.

Structure of Tumor.—The tumor is a glioma, growing rapidly. Every region of the tumor examined shows numerous fibrils staining differentially by the methods of Weigert and Mallory for neuroglia. Mitoses in the tumor cells are frequent in some regions. Cells with two polar nuclei and cells with several nuclei are common in all regions; neuroglia fibrils stand in close association with many of these multinucleate cells. Centrosomes, or centrosome-like structures, are demonstrable both in the dividing cells (which are caught as a rule in the spireme phase) and in resting cells. The dots occur in pairs or in larger numbers up to eight. The dots vary in distribution. The pairs midway in the cell-body between two polar nuclei occasionally suggest the mid bodies in the end phase of some forms of cell division. In other cases it would seem difficult to call them anything except centrosomes. At times the dots have a more diffuse distribution in the cell-body, and their function can hardly be assigned. In all loci the dots fail to be quite spherical but are rounded and rod-shaped. The dots in pairs, which most resemble centrosomes, are biscuit-shaped. The dots do not occur in great numbers or in the arrangement characteristic of the tumors regarded as of ependymal origin. There is nowhere in the tumor a tendency to the formation of canals or ependymal cysts.

Besides displaying signs of rapid cell-division, the tumor is malignant in another sense, unusual for gliomata. This glioma breaks the usual rule that gliomata fail to invade non-nervous tissues. This is evident both from the gross description of the nodule in the right rostral region and from the presence of islands of neuroglia, clumps of neuroglia cells, single neuroglia cells, and wandering neuroglia fibrils in many places in the pia mater beyond the main line of contact between the tumor and the surrounding tissue.

But, although the tumor is rapidly growing and infiltrates the connective tissues as well as the nerve tissues, there is no evidence of true metastasis, such as has been reported by Mallory[2] in a glioma which took its rise outside the nervous system. There is also no evidence of selective growth along connective tissues, as has recently been shown by Mallory to occur in a case examined at the Children's Hospital by Dr. H. C. Low. The present glioma may, however, be ranked as more malignant than most cerebral gliomata, since it shows in a minor degree the property of infiltrating the connective tissues.

A more detailed account of the tumor follows:

The vascular supply of the tumor is free. Thrombosis of the veins is frequent and is probably responsible for much of the necrosis and cyst-formation in the interior of the tumor. In a few places there is evidence of early overgrowth of intimal cells in the small veins, although the surrounding tissues are still well-nourished. More frequent than the endothelial proliferation is a proliferation on the part of adventitial cells. Mitoses among adventitial cells are fairly frequent in a few places near the outer border of the tumor under the pia mater.

What may be termed the stroma of the tumor is a fairly dense fibrous tissue which is so deep in places as to suggest the remains of old sulcal processes of pia mater. Islands of dense fibrous tissue, several mm. in diameter, are brought out by the connective tissue stain deep in the interior of the tumor (Plate VII, Fig. 4). The term stroma is warranted furthermore by the occurrence of small islands of densely fibrillar neuroglia. (Plate VII, Figs. 1, 2, detail in Fig. 5) in many places in the pia mater, and in fibrous processes stretching in from the pia mater. With the lower powers, it cannot always be shown that these apparent neuroglia islands are actually cross-sections of processes of the tumor mass. Many of the islands can be shown in serial sections to be in continuity with the tumor mass. With the higher powers, this question becomes less important, since throughout the fibrous tissue in the neighborhood of the islands or processes are numerous isolated neuroglia cells or pairs or rows of cells enclosed in fusiform cages of neuroglia fibrils (Plate VIII, Figs. 5, 6, 8). The isolated cells, or cell-groups limited by single cylinders of fibrillæ, are set as if in definite clefts of the fibrous tissue, but they fail to grow in lymph or vessel spaces. Besides the isolated neuroglia cells and cell-groups, scattered neuroglia fibrillæ can be found wandering off straight or slightly curved through the wavy fibrous tissue. It may be that these fibrils wandering free through the fibrous tissue (Plate VIII, Fig. 5) are related with the peculiar invasive property shown by this tumor. This cannot be proved. The chances are that the fibrils grow blindly along lines of least resistance. No alteration in the character of the connective tissue in these regions can be made out.

---

[2] F. B. Mallory, Three Gliomata of Ependymal Origin, Journ. Med. Research, 1902, Vol. VIII, pp. 1-10, and A Contribution to the Classification of Tumors, Journ. Med. Research, XIII, 2, January, 1905.

The tumor varies somewhat in the character of cells met in different regions. There are sudden transitions in character in two loci, at the pia mater and adjacent to the characteristic cystic spaces. Elsewhere, though there is considerable variety, the transitions are gradual. The sharp boundaries of the tumor as it meets the pia mater and the definite outlying masses of neuroglia have been described. The cystic spaces filled with fibrin or granular coagulum are occasionally marked off sharply from the well-nourished masses and exhibit indentations corresponding with adjacent pervious vessels (Plate VII, Figs. 1 and 2). Sometimes, between the free fluid of the cyst and the densely fibrillar subpial tissue there is interposed a looser but still fibrillar tissue which is apparently prevented from complete solution by a few strands of vascular tissue (Plate VII, Fig. 3).

IV. Summary.

1. Man of forty one, dying ten weeks after onset of symptoms pointing to cerebral disease, showed three apparently discrete nodular lesions of the right frontal lobe, one of which had pierced the pia mater of the longitudinal fissure and invaded the left rostral convolution.

2. Examination of the hemorrhagic and edematous tissue of the medullary center beneath the nodules showed bands of tissue like that in the nodules. If the tumor started from one focus in

the medullary center, the extent and character of the lesion may be due to rapid growth, unequal along different radii. Thrombosis accounts for the necrotic and cystic center of the mass.

3. The tumor is a glioma, rapidly growing and malignant in a sense unusual for cerebral gliomata, in that it invades non-nervous tissue.

DESCRIPTION OF PLATES.

Plate VII, Figure 1.

Outer border of tumor nodule, overlaid with a thin sheet of pia mater and pierced by a stout process of fibrous tissue which contains islands of neuroglia. Cystic spaces in tumor, containing fibrin. Phosphotungstic acid hematein with ferric chloride differentiation.

Plate VII, Figure 2.

Outer border of tumor nodule. Large central cystic space, with overlying subpial shell of tissue thrown into folds. Rich supply of small vessels with deep adventitial tissues. Stout process of pia mater, containing small islands of new-growth. Stain as above.

Plate VII, Figure 3.

Outer border of tumor nodule. Above, pia mater with vessel. Next, the densely fibrillar outer shell of the tumor, sharply marked off from less well-nourished clear tissue with fewer fibrils. Below, cystic space. Stain as above.

Plate VII, Figure 4.

Interior of tumor. Characteristic island of fibrous tissue or deep process of pia mater with numerous vessels. The whole surrounded by new-growth. The fibrous tissue here stains dark. Anilin blue connective tissue stain.

Plate VIII, Figure 5.

Detail from section figured in Plate VII, Figure 1. Slender processes of fibrillar tissue, imbedded in connective tissue which is left unstained (by ferric chloride differentiation after staining with phosphotungstic acid hematein). The connective tissue is everywhere penetrated by isolated neuroglia fibrils, often some distance away from their cells of origin.

Plate VIII, Figure 6.

Cells isolated in fibrous tissue of a process of pia mater. Two nuclei, with overlapping ends and without demonstrable cell-bodies, enclosed in a fusiform cage of coarse agglutinated fibrils. Phosphotungstic acid hematein.

Plate VIII, Figure 7.

Imitation of Golgi picture in very deeply stained phosphotungstic acid hematein preparation from tumor.

Plate VIII, Figure 8.

Young neuroglia cell with fibrils faintly shown (not stained by phosphotungstic acid hematein). Six dots in interior of cell body at a distance from nucleus.

Plate IX, Figures 9, 10, 11, 12.

Cells showing one or more dots in cell-bodies, sometimes enclosed in pale space (Figure 12).

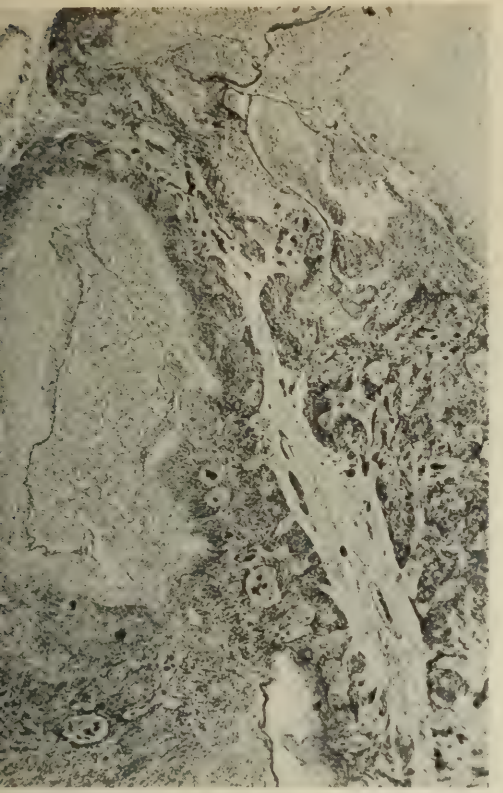
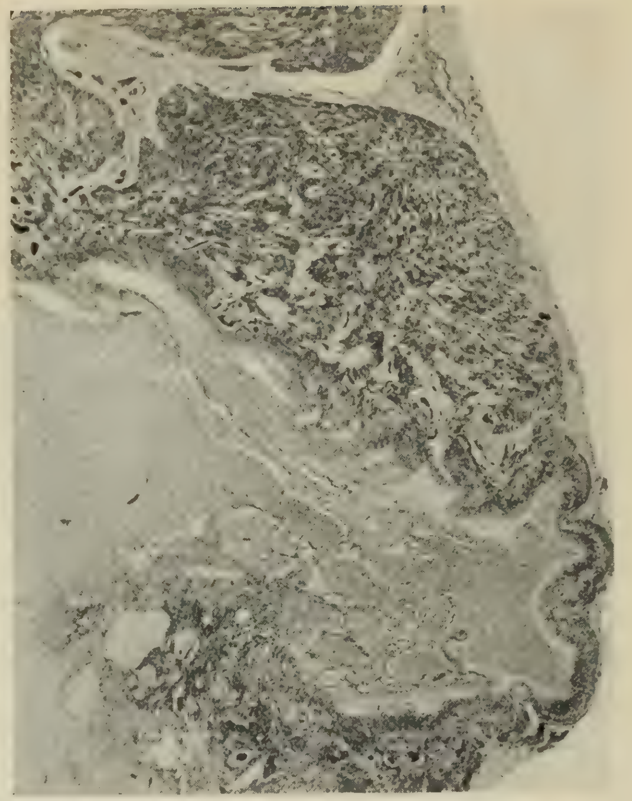


FIG. 1.



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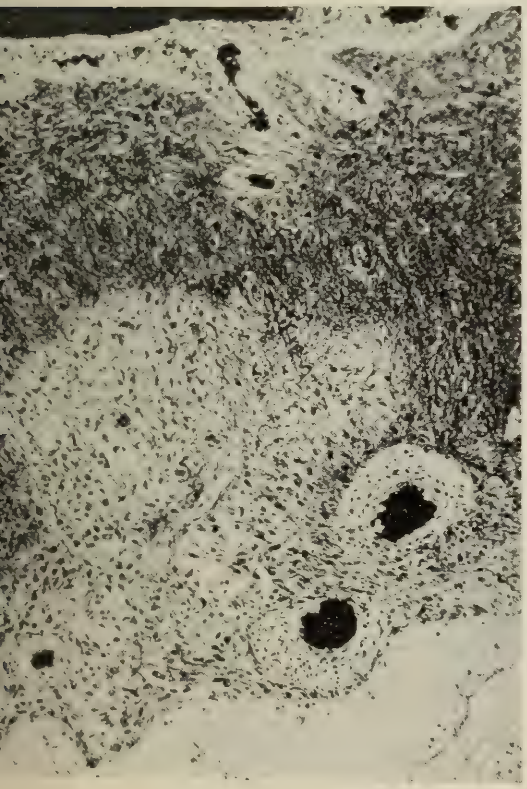

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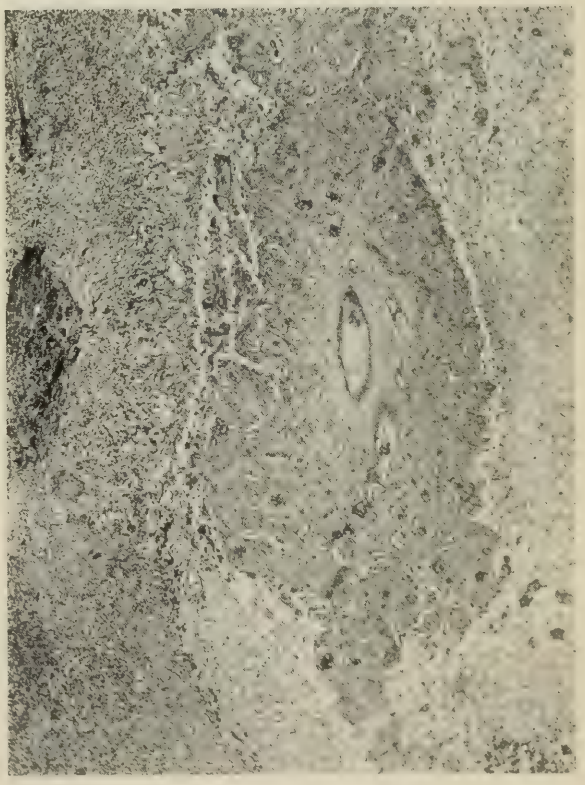

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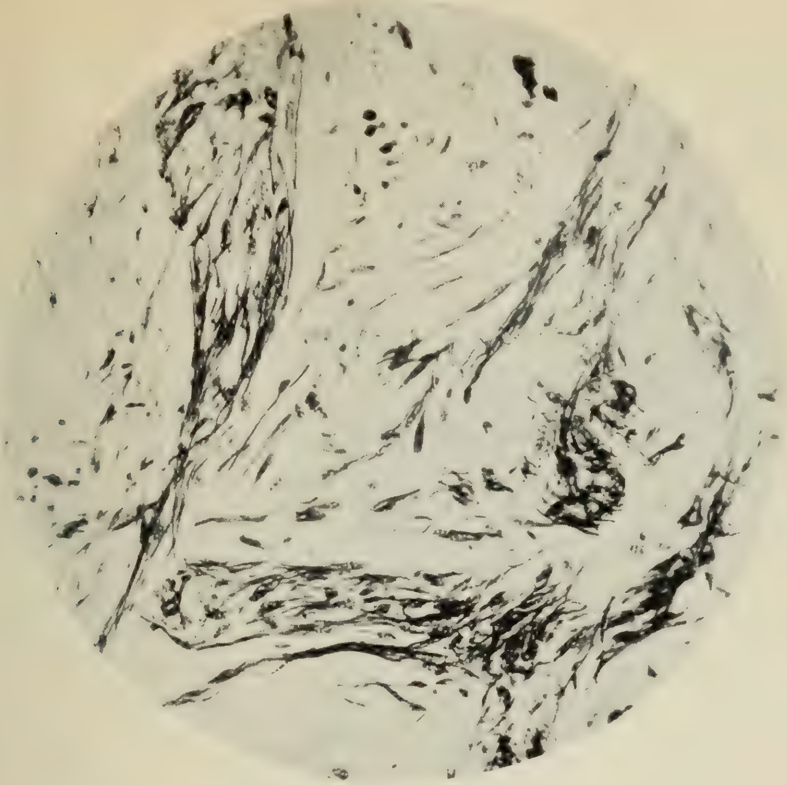

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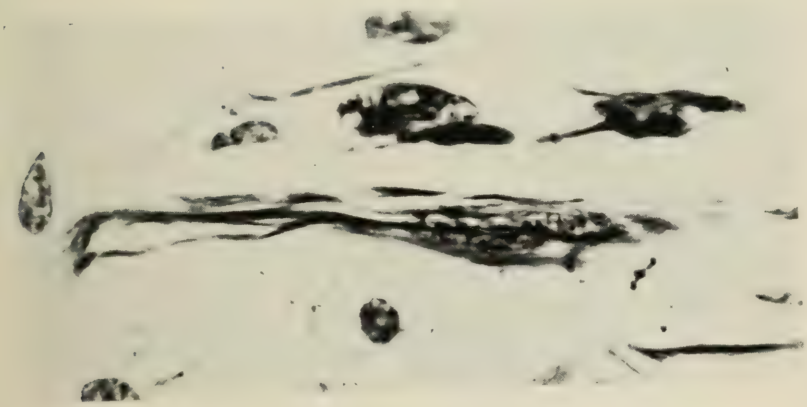

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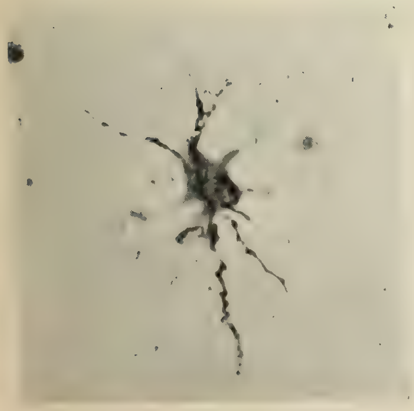

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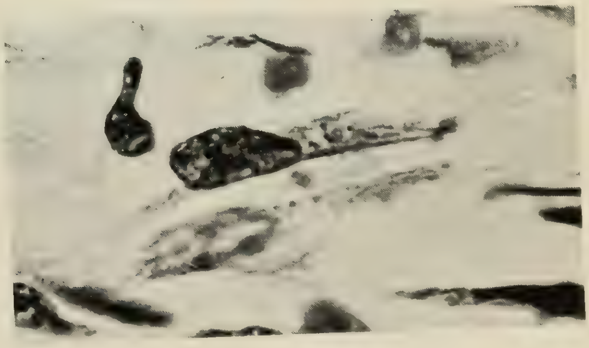

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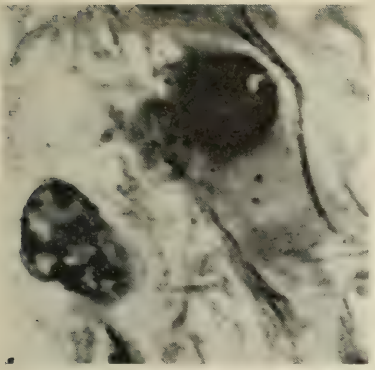

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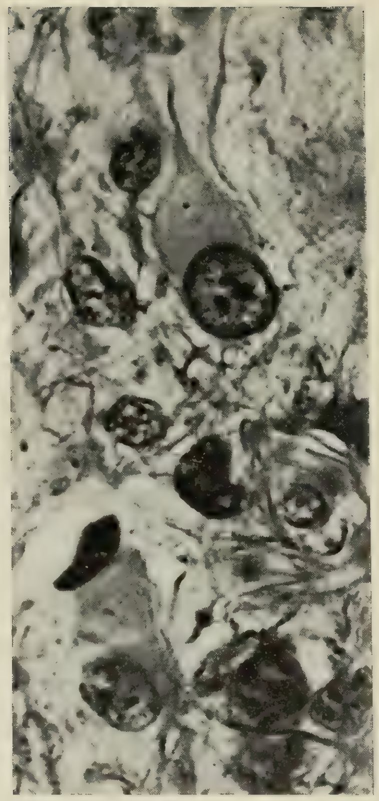

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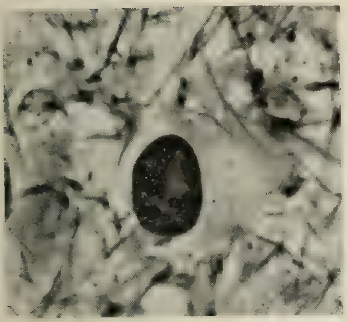

FIG. 11.

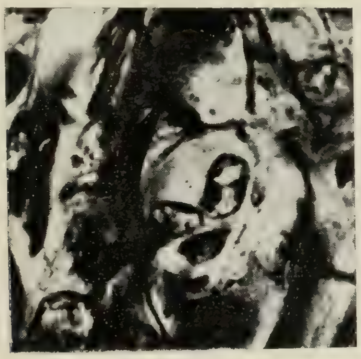

FIG. 12.

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CONTENTS.

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A. N. Collins and E. E. Southard.

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CONTENTS.

VIII. THE FUNCTION OF TONICITY IN HUMAN ISOHEMAGGLUTINATION.

F. P. Gay.

(From the Journal of Medical Research, xvii, 3, December, 1907.)

IX. THE DETERMINATION OF THE ALEXIC ACTIVITY OF HUMAN BLOOD SERUM.

F. P. Gay and J. B. Ayer, Jr.

(From the Journal of Medical Research, xvii, 3, December, 1907.)

X. ALEXIC ACTIVITY OF THE BLOOD SERUM OF CADAVERS.

F. P. Gay.

(From the Journal of Medical Research, xvii, 3, December, 1907.)

NOTE.

These papers represent work done during two years, 1906 and 1907, in connection with the BULLARD PROFESSORSHIP in Neuropathology in the Harvard Medical School.

The work would have been impossible, had it not been for the liberal research policy of the DANVERS STATE HOSPITAL for the Insane. The resources of the Danvers laboratory have been made available through the courtesy of Dr. Charles W. Page, Superintendent, acting for the Board of Trustees.

The work has further been aided by donations from a fund established by the late ARTHUR W. BLAKE, and Dr. Gay's work has been aided by a grant from the PROCTOR FUND.

The technical work has been done in part at Danvers, in part in the new laboratories of the Harvard Medical School.

A committee composed of Drs. W. T. Councilman, J. J. Putnam, F. B. Mallory, W. N. Bullard, and E. E. Southard has had general charge of the work.

Although not strictly neuropathological, the studies of Gay, Gay and Southard, Gay and Ayer are included because of their relation with work in progress.

OUTLINE

OF

NEUROPATHOLOGY

BY

E. E. SOUTHARD

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OUTLINE OF NEUROPATHOLOGY.

CONTENTS.

PAGE

I. GENERAL PRINCIPLES 1
- PECULIAR FEATURES OF NEUROPATHOLOGY . 1
- CHEMICAL PATHOLOGY 2
- STRUCTURAL ELEMENTS 4
- CENTERS AND TRACTS 7
- PARENCHYMATOUS AND INTERSTITIAL DISEASES, 9
- EFFECTS OF INJURY 12
  - Causes of Death 13
  - Losses of Substance 14
  - Disorders of Circulation 15
  - Inflammation 20
  - New Growths 22
- REPAIR AND REGENERATION 25

II. STRUCTURAL DIAGNOSIS 26
- METHODS OF EXAMINATION 26
- INTERPRETATION OF GROSS APPEARANCES . 27
- DISEASES OF DURA MATER 28
- DISEASES OF PIA MATER 30
- NEUROGLIA AND EPENDYMA 31
- MALDEVELOPMENT 33
- FOCAL LESIONS 36
- FIBER DEGENERATION 38
- THE AXONAL REACTION 38
- SECONDARY DEGENERATIONS OF CEREBRUM . 39
  - Cerebral Hemorrhage 39
  - Cerebral Palsy of Children 40
  - Cerebral Monoplegia and Cortical Epilepsy . . 40
- CEREBELLAR LESIONS 41
- DISEASES OF PONS AND BULB 43
- TRANSVERSE LESIONS OF SPINAL CORD . . 44
- UNILATERAL LESIONS OF SPINAL CORD . . 45
- SYSTEM DISEASES 45
  - Tabes Dorsalis 45
  - Progressive Muscular Atrophy 47
  - Amyotrophic Lateral Sclerosis 47
  - Combined System Disease 48

PAGE
SYRINGOMYELIA 49
GENERAL PARESIS 49
ACUTE ANTERIOR POLIOMYELITIS 50
MULTIPLE DISSEMINATED SCLEROSIS . . . 51
EPILEPSY 52

III. NEUROPATHOLOGICAL PHYSIOLOGY . . 53
THE NEURONE THEORY 54
THE REFLEX ARC 56
Reflex Acts 56
Synapses 57
Functional Changes in Reflex Arcs 58
GENERAL AND FOCAL SIGNS AND SYMPTOMS . 60
Motor Data 63
Sensory Data 65
Disorders of Reflex Movement 66
Vascular and Glandular Disorder 70
LOCALIZATION IN NERVOUS DISEASES . . . 70
Peripheral Nerves 72
Sympathetic Nerves 74
Spinal Cord 74
Pons and Medulla 76
Basal Ganglia 79
Cerebellum 79
Cerebral Hemispheres 82

IV. NUMERICAL DATA 88

V. REFERENCES 91

OUTLINE OF NEUROPATHOLOGY.

The present outline deals with the special pathology of the nervous system. The outline starts with (1) a review of some GENERAL PRINCIPLES, and proceeds to take up (2) the structural side of neuropathology (ANATOMICAL, HISTOLOGICAL, and FIBER-TRACT DIAGNOSIS), and (3) the functional side (NEUROPATHOLOGICAL PHYSIOLOGY) with special reference to the underlying lesions. Separate sections contain (4) NUMERICAL DATA, and (5) REFERENCES.

I. GENERAL PRINCIPLES.

The principles of general pathology are less readily applied to the nervous system than to the main organs of the trunk. The complications of neuropathology are several. The first in importance of these complications is the special principle of SECONDARY DEGENERATION, a process undergone by nerve fibers when separated from their cells of origin. Through the working of the principle of secondary degeneration, any focal injury to the nervous system may produce far more than focal effects. The second peculiarity of the nervous system is the occurrence in the cerebrospinal axis of a fresh kind of interstitial tissue, the NEUROGLIA, not found elsewhere. And, although the neuroglia reactions (cellular and fibrillar gliosis) present many analogies with the characteristic reactions of mesoblastic connective tissue, yet the neuroglia reactions are more delicate than the latter and may or may not coexist with them. A third very striking thing is a histopathological complication, viz.: the extensive development of PHAGOCYTIC CELLS of the mononuclear type in almost all types of lesion at some stage. Thus each type of tissue in the nervous system (parenchyma, neuroglia, and mesoblastic framework) has its special complications (secondary degeneration, cellular and fibrillar gliosis, abundant phagocytosis).

On the physiological side, complications increase. Whereas the main organs of the trunk are composed of great numbers of similar units, the elements of the cerebrospinal axis differ much among themselves. This VARIETY OF ELEMENTS is exemplified in the sixteen or more types of cerebral cortex which can be somewhat readily distinguished microscopically, or again, in the half-dozen or more separate types of cell in the cerebellum. Moreover, in those regions of the axis which are composed of similar units, it is not possible to argue that these similar units resemble one another in function. This great variety of elements in structure and function is related with a second physiological peculiarity of the nervous system, the character of so-called nerve centers. THE NERVE CENTER IS NOT NECESSARILY AN ANATOMICAL FOCUS. The working of a nerve center may depend upon simultaneous activities in several cells at remote points. Both the histological and chemical variety of cell elements and the peculiar plurifocal character of nerve centers are instances of the extraordinary division of labor which has occurred in the cellular development of the nervous system. Many cells have no single functions, but are indispensable to the performance of various total functions. Some of these functions consist of direct stimulations to activity, and therefore present analogies with other orderly but non-nervous processes in the body. Unique, however, are the INHIBITORY FUNCTIONS of several centers and regions. Neither histology nor histopathology is able to point out special tissue peculiarities which underlie the inhibitory functions.

CHEMICAL PATHOLOGY.

Like the other tissues which are termed solid, the nervous system is composed largely of WATER. Thus the gray matter of adult man is stated to contain more than 83 per cent of water. The white matter contains somewhat less water than the gray, and hence the spinal cord contains less than the brain, and the nerves least (about 60 per cent). The specific gravity is given as 1.035.

The most important of the solids occurring in nerve tissue are (1) the proteids, (2) the phosphorized fats, and (3) the cerebrosides. Besides these, cholesterin occurs in considerable quantity, with nuclein, neurokeratin, gelatin, various extractives, and inorganic salts.

More than 50 per cent of the solids found in the gray matter of adult man is PROTEID. The proportion so changes in the rest of the nervous system that we roughly describe (*a*) the amount of gray matter, (*b*) the amount of water, and (*c*) the percentage of proteid in the solids, as varying directly with one another. The proteids of nerve tissue include globulins and a nucleoproteid. One of the globulins coagulates at 47°, the other at above 70°.

The phosphorized fats (lecithans, phosphatides) include several groups, of which most is known about LECITHIN. Lecithin decomposes into stearic (or other fatty) acid, glycerophosphoric acid, and choline. Choline, tested for in the cerebrospinal fluid or in the blood, is taken as evidence that nerve tissue has undergone decomposition. The choline test has been used to some extent to determine whether a case is "organic" or "functional," that is, whether active degeneration is or is not going on in the nervous system.

The cerebrosides are glucosides from which GALACTOSE may be obtained.

The CEREBROSPINAL FLUID, clear and watery, sp. gr. 1.004 to 1.007, contains a trace of proteid, a substance reducing Fehling's solution, and a minute quantity of choline. The fluid is said to be secreted at the rate of more than half a liter per diem (observation on patient with spontaneous dripping of cerebrospinal fluid through nose). The substance is derived doubtless from two sources, the lymphatics of the pia mater and the lining cells of the choroid plexuses. The fluid from the choroid plexuses may be regarded as a secretion rather than a transudation. Fluid collected during forced expiration or abdominal compression has more the character of a transudate, being poorer in solids than the fluid passed out under normal conditions. Fluid from cases of SPINA BIFIDA and of HYDROCEPHALUS has a little higher percentage of solids. The cerebrospinal fluid is hypertonic with respect to ordinary serum. Various drugs pass from the cerebrospinal fluid to the blood.

The chemical changes of the living nervous system are probably not attended with a change of reaction. The human brain, and especially the gray matter, rapidly becomes acid to litmus (lactic acid). One chemical sign of activity in the nervous system is the choline which is found in traces in normal cerebrospinal fluid. Moreover, normal salt solution quickly extracts choline from fresh nerve tissues, and more from the gray than the white matter. Fatigue is difficult or impossible to demonstrate in the case of nerve fibers, either medullated or non-medullated. Perhaps there is no more delicate sign of chemical change in the nervous system than the dissolution of Nissl granules (tigroid bodies) of certain nerve cell types in various abnormal states. An endeavor has been made to connect the "fever change" of nerve cells with the coagulation point of one of the globulins of nerve tissue. The globulin which coagulates under ordinary conditions at 47° was found to coagulate even at 42° when maintained at that temperature for several hours.

Some points in the chemical pathology of GENERAL PARESIS of the insane have been made out. The cerebrospinal fluid in general paresis is more abundant than in the normal brain, since it may be drawn off from the increased space yielded by the atrophied brain, and is richer in solids from an excess of proteids. Fibrinogen remains absent. The proteids are albumin and nucleoproteid. The substance reducing Fehling's solution which is found in normal cerebrospinal fluid falls out as a rule in the fluid of general paresis. Choline is found in abundance. The blood of paretics is found to contain choline during a seizure. Other nervous diseases in which there is disintegration of tissue yield choline also.

Phosphorus determinations have been made in degenerated nerves and cord tissue. The destruction of lecithin in degeneration correspondingly lowers the amount of phosphorus.

STRUCTURAL ELEMENTS OF THE NERVOUS SYSTEM.

The neurochemistry summarized above is based upon analyses which take little account of the separate cell types and fiber types of the nervous system. Consequently at the present day chemistry is far from affording a basis for the physics of the reception, transmission, and discharge of nervous impulses, the physics, namely, of the reflex arc. At the present day histology yields more data for use by neurophysics than those yielded by neurochemistry.

The histological data are of several sorts. It is possible to distinguish separate kinds of (1) end organs for the reception of nerve impulses, (2) fibers for the transmission of nerve impulses, (3) gray centers for the modification of rate, the distribution, and the inhibition of nerve impulses, and (4) end organs by which discharge of nerve impulses is effected. Thus a number of points are now known concerning the histology of reflex arc mechanisms.

The structural elements with which we deal are

1. The *nerve cell and dendrites* and
2. The *nerve fiber* (axis-cylinder) *and sheaths.*

1 and 2 are nowadays coupled and designated as *neurone* (neuron). The neurones are conceived as units, by some writers as developmental units, by others as trophic units, by others as physiological or functional units. From the pathological point of view the neurone theory of nerve structure is useful as expressing the vital relations of the cell and the fiber, namely, the death of the fiber following death of the cell (secondary degeneration) and the alteration of the cell when separated from the fiber ("axonal" reaction of Nissl); these changes are described under the head of histological diagnosis.

3. The *anatomical nucleus* (*e.g.*, oculomotor nucleus, cuneate and gracile nuclei), a focal collection of homologous nerve cells having as a rule homologous functions. But, although the association of similar nerve cells in a given area is a frequent mechanism for the reception and discharge of impulses, it must be remembered that such mechanisms are not always unifocal. The physiological nerve "center" is not necessarily an anatomical nucleus. In order to set in action many of the higher functions, it is probable that a plurifocal rather than a unifocal stimulation is required. No single anatomical nucleus superintends, it is likely, the speech function.

4. The *fiber system* (*e.g.*, optic radiation, pyramidal tract, cochlear nerve), a collection of homologous fibers associated with an anatomical nucleus and relating it with another anatomical nucleus or with the exterior.

It can be seen from their composition that the anatomical nuclei (3) and their appertaining fiber systems (4) may be regarded as neurone systems. Thus injury to an anatomical nucleus will bring about secondary degeneration of the appertaining fiber system, whereas section or other injury to a fiber system will bring about reaction in the cells of the appertaining anatomical nucleus.

Moreover, as an effect of chronic "intoxications" or under conditions not well understood, these mechanisms may undergo changes in characteristic ways (see tabes dorsalis, amyotrophic lateral sclerosis, and other examples under the head of *system diseases*).

5. The *conduction path* (*e.g.*, precentral gyri — pyramidal

tract — anterior horn — motor nerve, sensory nerve — dorsal column — cuneate nucleus — fillet — gray matter of thalamus — corona radiata — sensory cerebral cortex), collections of fiber systems set end to end with anatomical nuclei interposed and serving to carry impulses for certain functions.

Diseases affecting conduction-paths in their totality fail to occur in the strict sense. Thus, if a given motor fiber system be destroyed and the cells of its appertaining anatomical nucleus (*e.g.*, in the anterior horn of the spinal cord) undergo the "axonal" reaction of Nissl, it is usually taken for granted that the change does not proceed further than the anatomical nucleus in question. Nevertheless, in some cases, whether from disuse or some trophic alteration, changes do sometimes follow in other fiber systems of the affected conduction path and are shown in the cells of the next anatomical nucleus (*réactions à distance*). Thus it is now maintained that the histological effects of an amputation may be followed, not alone within the range of the peripheral neurone (as axonal reactions in the anterior horn, conceived to be related nutritionally with the cut fibers), but also at the cerebral cortex through remote effects upon the central (corticospinal) neurone (as *réactions à distance* in the cells of some part of the precentral gyrus). In this sense, conduction-path diseases may occur, and of course it is readily possible that chronic "intoxications" may affect together both central and peripheral fiber systems.

6. The *projection system* (an apparatus composed of the two great motor and sensory conduction-paths which serve to connect the periphery with the cerebral cortex). The projection system becomes of paramount importance in the higher animals. Lesions of the receptive leg of the projection system alter or remove sensory or trophic data, and lesions of the discharging leg of the projection system remove or alter the capacity for motor or glandular discharge. Nevertheless, the visible or demonstrable effects of both kinds of lesion are discharge effects in many cases. Thus the tabetic, receiving altered sensations from the periphery on account of lesions in his dorsal columns, exhibits striking effects in his motor functions. The objective effects (where the term objective is taken to mean demonstrable as opposed to reported or felt) of most lesions, wherever set, are motor effects.

7. The *association and commissural systems* (*e.g.*, fasciculus

fronto-occipitalis, corpus callosum, white commissure of spinal cord), apparatus serving to connect the parts of the projection system with one another for coördinating functions or for modifying them. The commissural systems connect symmetrical parts of the nervous system. The association fibers run fore-and-aft or obliquely. Whereas lesions of the projection system characteristically produce diseases with superficial alterations of motion (the neurologist's diseases), it is sometimes maintained that differential lesions involving the association system only might well produce mental diseases (in which the superficial alterations of motion are not characteristic). Such differential lesions have not been proved to exist. To state that mental diseases are strictly speaking association-tract diseases is to state only a part of the the truth.

CENTERS AND TRACTS.

The central nervous system consists of parallel and interlacing tracts of medullated fibers and of voluminous gray centers interposed between the termini of the tracts. The fiber tracts permit linear conduction only, whereas the gray centers effect, besides an end-to-end conduction between tracts, also multiple cross-conductions, in virtue of which indirectly any two tracts may be made to intercommunicate.

Although the nervous system throughout presents this fascicular structure, yet the bundles are far from being on one level of importance. It is conceivable that no single fascicle of the central nervous system is essential to the performance of its functions, on account of the manifold switching of impulses made possible by cross-conductions through the gray centers. Moreover, there is one great group of fiber fascicles which may be quite cut out of function without impairing vital activities — the association tracts of the brain. In fact, in the lower orders of animals no such system is developed.

To the great group of association tracts, which appear to form a specialized apparatus for elaborate cross-conductions between gray centers, may be opposed the group of fiber fascicles known as the projection system (motor and sensory tracts). The fascicles of the projection system are interposed, not between gray center and gray center, but between skin and voluntary muscles or between eyes and glands or between mucous membranes and the sympathetic system, and so on. The fascicles of the projection system serve to unite functionally various non-nervous structures. For a complete projection system but one loop is theoretically necessary with a center for intercommunication. As it happens, however, in man and the higher animals various gray centers are interposed at lower levels, forming shorter loops. These various fascicles between centers are subject individually to disease ; and the different combinations of disease which are for some reason confined to the tracts and centers are known as system diseases. The system disease is then, in a sense, a focal disease of the nervous system ; but the foci are linear, extensive, not related with the distribution of the arterial tree, anatomically and physiologically well defined. The neurone theory has been offered as the key to an explanation of these diseases. I have here presented the diseases objectively.

Focal injury to the adult nervous system produces more than focal effects. Remote regions are rapidly involved in what has been termed a secondary degeneration. In a case of focal lesion the tracts showing secondary degeneration will be characterized as follows :

1. The degenerated path runs out of the region of injury and is proportional in number of fibers to the elements of the destroyed area.
2. The area of degeneration does not spread by contact in its course with other areas. In case the degenerated path splits, the total cross-section of degenerated fibers remains the same and the area between remains intact.
3. The process of degeneration shown is at the same stage throughout the degenerated path.
4. The changes in the gray center corresponding will affect only the appropriate cells. Adjacent nerve cells fail to become involved.

It is evident, therefore, that regular and systematic remote changes are wrought by destruction of isolated parts of the nervous system. Similar extensive changes of the same general character are found in cases where there is no evidence of destructive lesion of isolated parts of the nervous system. The cause of these extensive fascicular diseases remains unknown. In many examples the history indicates a slowly acting cause. Older writers were content with the degenerations as primary or idiopathic. Modern writers mention poisons elaborated within the body, the persistent toxine of syphilis, or a combination of these as causes for certain forms. A group known as the combined system diseases has been related with pernicious anemia. Repetitions in successive generations have been noted in some forms.

The application of this conception of the gray centers and white tracts to the physiological conception of the nervous system as a structure designed to combine numerous reflex arcs is taken up in Section III.

PARENCHYMATOUS AND INTERSTITIAL DISEASES OF THE NERVOUS SYSTEM.

End organs, fibers, cells of origin, tracts, anatomical nuclei, paths of conduction, projection, and association go to make up the parenchyma of the nervous system. This parenchyma forms a physical apparatus designed to receive, transmit, discharge or inhibit nerve impulses.

Like the other parenchymal structures, the nervous system is provided with a nutritive apparatus and with supportive structures. We may associate the nutritive and supportive tissues under the name interstitial.

It is possible to divide the diseases of the nervous system logically into parenchymatous and interstitial diseases. Actually it will be difficult to find pure examples of the two types, because disease in either tissue group will react upon the other. It will be as hard to find a purely parenchymatous or a purely interstitial disease in the nervous system as in, for instance, the kidney. This difficulty increases with the duration of the injury.

In common with the other parenchymal structures, the nervous system is subject to several "interstitial" diseases, thus to circulatory disorders, exudative lesions, repair processes, new growths, and the deposition of degenerative products. So far, however, these interstitial diseases of the nervous system find parallels elsewhere in the body. Thus hemorrhages, embolic or thrombotic infarction, diffuse inflammations, abscesses, cicatrices, secondary nodules of carcinoma, pigmentation, are found in other systems.

The most important group of interstitial diseases of the central nervous system — the GLIOSES — is not shared by the other systems of the body. The neuroglia tissue to a large extent fills the space between the mesoblastic tissues and the nerve cells and fibers. There are normal variations in the amount of neuroglia in different parts of the central nervous system. Two types are distinguished: (1) ependyma, (2) fibril producing neuroglia. The satellite cells about the nerve cells may perhaps be classed as a third neuroglia cell type, non-fibril-producing. Mitoses have been observed in satellite cells in cerebrospinal meningitis.

(1.) The ependyma of the ventricles and of the central canal shares in several diseases. Small neuroglia scars, composed of neuroglia fibrils with quiescent cells of origin, are found in the floor of the fourth ventricle or generalized in other ventricles in general paresis of the insane as well as in a variety of other conditions. These *ependymal granules* are sometimes thought to be due to the reaction following multiple minute breaks in the ependyma, perhaps consequent upon alterations of ventricular pressure. In other cases the granular ependymitis is perhaps due to irritation by materials in the ventricular fluid.

A similar process in the central canal of the spinal cord is apt to lead to occlusion (*central gliosis* of the spinal cord). A degree of such change is well-nigh normal in the adult human spinal cord. The canal is obliterated. A group of cells similar to ependymal cells remains, and in the cytoplasm of some of these cells occur groups of dots like the basal dots in ependymal cells having a free ciliated surface.

Subordinate small canals or cavities lined with ciliated ependymal cells are sometimes found in the neighborhood of the posterior horns of the lateral ventricles and in the floor of the fourth ventricle. These *ependymal cysts* are regarded as of developmental origin. They are to be distinguished from the neuroglia-lined (but not ependyma-lined) cavities found developing from the posterior horns of the spinal cord (syringomyelia).

(2.) Of far greater general importance are the changes in the neuroglia tissue at large. The tendency of this change is to the formation of indurated areas or *scleroses,* in which the mesoblastic tissues may play little or no part.

The general process of *gliosis* (overgrowth of neuroglia tissue) resembles the general process of fibrosis in the mesoblastic tissues. We distinguish two phases in the overgrowth — a cellular and a fibrillar phase.

Cellular gliosis antedates the fibrillar form. Both types are found in progressive lesions, and it may be possible in single cases to observe a complete series of the changes.

Cellular gliosis comprises the active changes in glia tissue up to fibril formation and may take place both with and without multiplication of the original cells. Even in the non-proliferative form it is not infrequent to find multinucleate cells which have not gone on to complete division.

In the non-proliferative form of cellular gliosis the cells swell, often more on one side than on the other of the nucleus, and develop cytoplasmic processes which do not as a rule branch. The borders of the neuroglia cell processes appear to alter their structure so that they assume the differential stains for neuroglia fibrils. Centrosomes are demonstrable in all stages of the process. Cellular gliosis is best demonstrated near early focal lesions. Similar changes with greater variation in nuclear pictures can be followed in some parts of primary or essential tumors of the nervous system (gliomata).

Fibrillar gliosis is the end stage of the process. The dimensions of the resulting induration or sclerosis depend evidently upon the number of neuroglia cells in the locus to start with and upon the degree or absence of cell proliferation. For example, the granule layer of the cerebellar cortex possesses normally little or no neuroglia fibrillar tissue, whereas the adjoining white matter has a considerable supply of fibril-producing cells. Consequently a focus of well marked gliosis of white matter in the cerebellum may be attended by next to no fibrillar reaction in the adjacent granule layer. However, in the case of destructive lesions of the granule layer, attended by neuroglia cell proliferation, there may be much more extensive fibrillar gliosis of the granule layer, partly from without.

The distinction between cellular and fibrillar gliosis is actually artificial. The reaction as a whole, comparable as it is to mesoblastic fibrosis (as in scar-formation), has a wide significance for the central nervous system. The process rarely transgresses the original limits of nerve tissue, though sometimes neuroglia promontories are found making out for short distances into the pia mater of very sclerotic spinal cords. Old ependymal granules and occasional nodules in the cerebral cortex may project as much as a millimeter from the general surface.

The current explanation of gliosis is that it is essentially a replacement process, an endeavor to fill space left by dying or dead cells. An irritative as well as a replacement gliosis may perhaps occur.

Gliosis is more delicate a reaction than its analogue, mesoblastic fibrosis. Losses of substance which would be readily supplied by mesoblastic overgrowths in other organs characteristically terminate in *cysts* in the nervous system. These cysts, although they exhibit the incapacity of the neuroglia to grow over large spaces, are lined by dense neuroglia tissue which accompanies vascular strands for some distance into the cavity.

The best demonstrations of gliosis are afforded by lesions severe enough to destroy or alter the nerve cells, yet not severe enough to alter the blood supply. Such lesions permit unusual activity of the neuroglia cells. It is evident that somewhat finer grades of lesion may be demonstrated in the central nervous system than in many organs.

The central nervous system thus yields two kinds of interstitial lesion, (1) mesoblastic lesions, (2) neuroglia lesions. The occurrence of these is described below. Their essential similarity has been shown in an early case of Pott's disease in a monkey. Areas of secondary degeneration in this case demonstrated, as is usual, an attempt at repair, consisting in active neuroglia changes with new fibril formation. At the same time analogous changes were demonstrated in the mesoblastic tissues which invest the degenerated nerve bundles of the cauda equina. Here like reactions ensue upon like destructive lesions; but the reactions occur in embryologically different tissues.

EFFECTS OF INJURY.

The effects of injury here considered are local effects. These effects, both acute and chronic, form a chapter in general pathology, with a few modifications. The local effects of injury to the nervous system stand in sharp contrast with the specialized effects of focal lesion upon nutrition and other activities in remote tissues. These latter remote effects form the classical material of neuropathology. The local effects are, however, considered first, because by their nature, extent, and duration they modify the remote effects.

The effects of injury are considered under the heads of the CAUSES OF DEATH, LOSSES OF SUBSTANCE, and, more particularly, DISORDERS OF CIRCULATION, INFLAMMATION, NEW GROWTHS.

Causes of Death.

The causes of death related with the nervous system may be divided into causes of sudden death and into such as act slowly or cumulatively.

Sudden death is sometimes due to direct injury to the nervous system, as by trauma, mechanical shock, or the electric current. In some cases no molar changes are detectable in the tissues. From other evidence it seems probable that death in these cases is due to direct or indirect action upon the medullary centers for respiration and circulation.

In other cases of sudden death, lesions are found, such as fracture of the skull with hemorrhage, extradural or subdural hemorrhage, single or multiple hemorrhages in the pia mater, laceration of the brain substance, internal hemorrhages due to ruptures of weakened or aneurysmal vessels, and ventricular hemorrhages. The mechanism of death in these cases also is assumed to be through an action upon the medullary centers, either through over-stimulation or through complete inhibition.

Focal lesions of the medulla or of the adjacent tissues may naturally effect sudden death through the same mechanism, and in these instances the fatal injuries may be exceedingly small (embolism of minute tissue-fragments, fat, or air).

In another group of cases of sudden death by intoxication, we do not look for molar changes, nor is our present technique able to discover finer changes. Death from chloroform inhalation, aconite, and prussic acid may be practically instantaneous.

Thus a closer examination of the causes of sudden death shows that we should more truly speak of the *medulla* than of the whole nervous system as *a capital organ.*

The importance of the medulla is brought out once more in those frequent slower deaths due to the general tendency of injured brain substance to undergo edema. Edema in the inextensible skull eventually compresses the medulla to a suspension of function which means death. Voluminous lesions which are enlarging at all rapidly within the cranium not only themselves encroach upon the intracranial space, but also produce edema which still more diminishes the available space. Laceratio cerebri, hemorrhage, infarction ("acute softening"), new growth, foreign body, depressed fracture may all produce edema which eventually proves fatal through pressure upon the medulla. The tendency to fatal issue varies directly, not so much with the volume of the active lesion, as with the rapidity of its development.

Akin to the fatalities from increasing edema is the still slower death from INTERNAL HYDROCEPHALUS. In internal hydrocephalus the excess of fluid is not in the brain substance, but in the ventricles. Under normal circumstances the ventricular fluid has a free escape by way of the foramen of Magendie to the subdural space of the spinal cord. If the foramen of Magendie is blocked by a tumor or a tissue overgrowth, it appears that the choroid plexuses continue to pass out fluid against pressure and dilate the ventricles to the degree of suspending medullary functions through heightened intracranial pressure. The foramina of Monro, the aqueduct of Sylvius, or even the intervertebral openings of the spinal canal may be blocked by tumors or tissue overgrowths and effect the same type of "acquired" internal hydrocephalus.

The evil effects of edema and of acquired internal hydrocephalus are reducible to the inability of the adult skull to expand. In the case of edema the surgeon interferes by trephining. Sometimes the surgeon thus relieves pressure. Sometimes the *hernia cerebri* which supervenes is so great as to nullify the surgeon's work. In the case of internal hydrocephalus, the surgeon may trephine and tap the lateral ventricles (*paracentesis*).

Besides these mechanical causes of death, numerous other agents operate. Of the many NEUROTOXIC AGENTS, some give no sign of their method of attack. Others produce diffuse fatty degenerations of the central nerve tissue ("*central neuritis*," where -itis does *not* imply *exudation*, but signifies rather *change*). These agents operate sometimes through the medulla, but sometimes produce a more generalized *exhaustion* with softening down of nerve tissue *in situ*.

Akin to exhaustion is the effect of *senile atrophy* upon the nerve tissue. But in exhaustion and in senile atrophy, as in numerous other conditions, the effects wrought upon the body at large are too general to admit specifying the lethal effect.

LOSSES OF SUBSTANCE.

As the section on causes of death shows, focal loss of medullary substance may be fatal. The effect of loss of substance elsewhere in the nervous system is not directly so dangerous. Transverse lesions of the spinal cord are dangerous on account of the trophic functions thereby suspended and on account of the ready occurrence of intractable bedsores. The higher the cord lesion, the more dangerous. Upper cervical lesion affects the phrenic nerve.

Just as the supramedullary centers have not always been of importance in vertebrate evolution, so, too, in man extensive deficiencies and losses of intracranial substance in many regions are quite consistent with life, if the accidents of hemorrhage and compression can be avoided.

Thus, in *senile atrophy*, the loss of from one-fifth to one-quarter of the brain substance by weight can be endured for years in a vegetative life. Moreover, much of that which remains is neuroglia tissue and non-nervous.

Similar relations hold in microcephalic idiots and in forms of *idiocy* showing focal deficiencies. The viability or non-viability in these cases depends not so much on quantity of brains as upon other conditions.

Acquired deficiencies of brain substance may be of great extent yet consistent with life. Extensive replacement of tissue by a cyst of softening, extensive encroachment on the intracranial space by tumors, extensive subdural hematomata with underlying cerebral atrophy, and microscopic changes rendering the greater proportion of cells functionless, are examples of acquired deficiencies of substance consistent with life. The “ crowbar case ” and innumerable extirpation experiments are further examples.

From the pathological point of view, the important fact here is the lack of extensive regeneration of central nerve tissues on account of their high organization. Moreover, neither the mesoblastic connective tissue nor the neuroglia tissue is at all able even to fill the space of any but small destructive lesions in the nervous system. Hence the frequency of cystic lesions in the nervous system as opposed to cicatrices.

The physiological compensation for such losses must depend upon an education of lower centers, or upon a shifting of the division of labor, or will fail.

Disorders of Circulation.

Heart disease and vascular disease react in general upon the nervous system by alterations of tension, which require readjustments of intracranial pressure, and by alterations of nutrition.

Acute cerebral *anemia* produces loss of consciousness and respiratory spasm. The heart action is slowed, the blood pressure rises, respiration ceases, the blood pressure falls, the heart action is hastened, and death ensues. The chain of symptoms resembles that of asphyxia. The visible effects are due to an excitation followed by paralysis of the bulbar centers.

Anemia of slower onset fails to produce the preliminary excitation of the bulbar centers.

The results of *hyperemia* must at length imitate the results of anemia, since the continuance of hyperemia must heighten intracranial pressure. Continued high intracranial pressure will eventually produce bulbar anemia with the same train of symptoms as above mentioned.

General anasarca yields an edema of the nerve tissues in many ways comparable with the edema of other organs.

Thrombosis of the venous sinuses is an occasional accompaniment of chlorosis.

The *focal diseases* of the nervous system produced by circulatory disease may be classed under the heads of *thrombosis*, *embolism*, and *hemorrhage.*

Thrombosis is prone to occur with *slowed circulation* (superficial cerebral veins, venous sinuses). *Dilated vessels* (aneurysmal basilar artery) may become thrombosed. Marasmus exhibits thrombi in various parts of the circulatory apparatus in the nervous system; but these *marantic* thrombi are doubtless due to slowed circulation from heart weakness.

The group of thrombi produced by immediate intravascular coagulation is theoretically distinguished from the group of thrombi produced by lesions of the vascular intima. The latter adherent thrombi occur in infectious diseases (especially pneumococcus meningitis and tuberculous meningitis) and in atheromatous arterial disease.

Embolism of tissue fragments from the heart valves or elsewhere is frequent. The brain ranks with the kidney and the spleen in frequency of embolism. Emboli which lodge in the normal circle of Willis may do no harm, on account of the free anastomosis of the larger vessels. The branches of the circle of Willis are, however, terminal arteries so that no collateral circulation can be established upon embolism into these branches.

Arteriosclerosis gives rise, by slow occlusion or by permitting thrombus-formation in various arteries, or by rupture, to similar and often multiple areas of white or red softening.

The areas of softening (encephalomalacia), whether of embolic or local origin, become somewhat rapidly pigmented in case they contain blood. The surrounding yellow zones gradually fade as the lesion grows older. The edema subsides, the loss of substance is only partially made good by organization, and the typical cyst of softening ensues, with its loose-fibered wall and brownish slightly turbid enclosed liquid. The cysts which follow white softening contain a colorless and almost clear fluid.

Aneurysms (preferably in the basilar and Sylvian arteries) occur and may remain undiscovered in the mass of subpial or subdural hemorrhage following their rupture. Miliary aneurysms should be searched for like miliary tubercles by teasing out and washing the vessels (for instance, the Sylvian arteries).

Voluminous hemorrhage (apoplectic) follows rupture of sclerotic arteries in the brain substance. The most frequently affected of the cerebral arteries is one of the lenticulo-striate branches (Charcot's artery of hemorrhage) of the central ganglionic system. Edema of the brain, flattening of the convolutions, and pressure about the veins follow; in many cases bleeding continues till the adjacent ventricular wall breaks and all the ventricles are speedily flooded. In other cases coagulation interposes, and a smaller local lesion remains which heals more after the fashion of an infarct. The importance of this typical apoplectic hemorrhage in the basal ganglia depends upon its effect on the fibers of the internal capsule. Thus, if the hemorrhage destroys the fibers of the anterior two-thirds of the posterior limb of the internal capsule, that is, resects the pyramidal tract, total hemiplegia of the opposite side of the body is sure to ensue. Smaller hemorrhages may pick out smaller fiber-systems, whereas larger hemorrhages may involve the upper sensory tracts as well as the motor tracts. At the time of the injury the effects of the hemorrhage are magnified by the surrounding edema; if healing takes place, the lesion diminishes in volume and fewer muscle groups and sensory areas are involved than at the outset. Cured or repaired hemiplegics may live for years and die of some intercurrent disease, often related, however, to advancing arteriosclerosis.

Besides voluminous hemorrhage due to arteriosclerosis, the brain and the cord exhibit multiple small hemorrhages in perivascular spaces which are due to manifold causes. Some of them are due to miliary aneurysms, some to sclerotic changes occurring in the distributing system of arteries, some to whatever conditions underlie the hemorrhagic diathesis, some to the toxines of acute infectious diseases (Staphylococcus pyogenes aureus, Bacillus typhosus), some to electric and mechanical shocks, and some possibly to unknown endotheliolysins. Hemorrhages, in part of mechanical origin, occur in leukemia, especially the lymphatic form.

There are few cases in which it is warrantable from brain findings alone to assert cerebral hyperemia or anemia. This is not to say that they do not occur in life.

In this place may be mentioned two diseases of the dura mater which are of immediate importance. Chronic internal hemorrhagic pachymeningitis consists in the successive deposit and organization of layers of hemorrhage in the inner meshes and on the inner surface of the dura. The pigmented membrane or the fresh hematoma may extensively compress the convolutions, shoving them away from the dura *en masse* with a broad wave-like surface. The condition occurs chiefly in old men.

The sinuses of the dura mater are the site of thrombosis. Marantic (autochthonous) thrombosis occurs frequently in the longitudinal and lateral sinuses of the very young and the old and in chlorosis. In the brain follow stasis, edema, hemorrhages, or even encephalomalacia. The seat of infective thrombosis is, as a rule, the lateral sinus opposite the sigmoid fossa of the temporal bone (following otitis media and interna).

Disorders of the lymph circulation are mainly shown in the ventricles and in the arachnoidal villi. Obstructions in the choroid circulation, notably in the vein of Galen, are often attended with internal hydrocephalus; but, as a rule, chronic inflammation or other occlusive change is found lower down in the ventricular system. Such mechanical obstruction at the foramina of Monro, the aqueduct of Sylvius, and at the foramina of Magendie and Mierjejewski will separately produce ventricular dilatation above the point of occlusion, provided that the lymph transudes as usual from the choroid plexuses. Below the lesion (tumor, organization of exudate in healed cases of meningitis and fracture of the base) the lymph flows away unimpeded to the subdural sheath of the spinal cord.

The circulation in the arachnoidal villi is impeded in chronic passive congestion of the sinuses. In certain cases the arachnoidal villi are themselves filled with blood. Their development varies, although irregularly, with age. In old subjects the villi may form a dense mat a few centimeters wide on both sides of the longitudinal sinus. Some villi grow very large and, sometimes devoid of dural sheath, lie in small cavities in the inner table of the parietal bone; such villi have been known to perforate the bone. They must be distinguished from multiple small true herniæ of cerebral substance, which are occasionally seen.

Anemic necrosis in the brain and cord is of the colliquative form. The dead tissue softens and swells into a mass of gray detritus which may be variously colored by blood. The detritus contains considerable myelin or material staining with osmic acid. Hemosiderin and iron-free pigments may occur in the area. Granule cells rapidly appear to aid in absorption.

Very small areas of colliquative necrosis may become thoroughly organized. The rule is partial organization, with cyst formation. The cyst fluid may be yellowish or brownish and slightly turbid, containing numerous fatty granule cells. The walls are uneven from the jutting in of vascular tufts surrounded by coarse and fine neuroglia fibrillæ. The older lesions show a slowly condensing capsule of neuroglia, with fewer and fewer neuroglia cells of the type in which cell bodies are evident.

Small hemorrhages into the brain substance are characteristically linear, dissecting the perivascular sheaths or running between fiber fascicles. In the clot hematoidin crystals and hemosiderin are demonstrable. Dissolved iron-containing pigment may be reprecipitated for a considerable distance from the original extravasation. Phagocytes are found containing blood globules and pigment. Reabsorption of perivascular hemorrhages is rapid; but pigment-bearing phagocytes are demonstrable long after the injury. The process of healing in destructive hemorrhage resembles that of anemic necrosis. Occasionally there may be found in the destroyed area dying nerve cells, whose shrunken bodies contain granules smaller than Nissl granules and staining by methods for neuroglia and fibrin.

Periarterial overgrowth of neuroglia may be found in cases with normal vessels, in arteriosclerosis, and in gliomata.

Hyaline degeneration is found in the media of small vessels in the brain and in the meninges in tuberculous meningitis and other conditions. This may be hard to distinguish from caseation. Some of these areas are partly calcified.

The intimal changes of arteriosclerosis are frequent. Subendothelial proliferation of intimal cells occurs in tuberculous and pneumococcal meningitis. Rapid and extensive intimal proliferation in meningeal vessels is characteristic of syphilitic meningitis.

INFLAMMATION.

General Features.

The ending "-itis" is extensively used in describing lesions of the nervous system of quite various origin (thus alcoholic polyneuritis, compression myelitis, parenchymatous-degenerative myelitis, granular ependymitis, traumatic, toxic, and bacterial encephalitis). The ending "-itis" *as used* virtually means "lesion of."

The course of exudation and repair in the nervous system exhibits peculiar features. The passage of fluid from the vessels is peculiarly swift and voluminous; and the edema may at times be remarkably transient. Diapedesis and small perivascular hemorrhages are frequent. The exudation of polynuclear leucocytes, though even and voluminous in the meninges, is somewhat rare in the brain substance itself except in large destructive lesions and in areas softened by edema. In epidemic cerebrospinal meningitis, the leucocytes wander considerable distances from the pial vessels. The leucocytes wander readily in either direction through an apparently intact ependyma. The most characteristic cell of various brain lesions is the large phagocytic or compound granule cell which accumulates often in extraordinary numbers about vessels and in cysts of softening. Many of these cells are of endothelial origin; mitoses are often demonstrable near vessels.

Besides the changes in and about the vessels, which nerve tissue shares with other tissues in inflammation, there are changes in the neuroglia of the central nervous system in inflammation. The neuroglia cells in the cortex and beneath the ependyma are increased in number. Mitoses in the glia are demonstrable in favorable cases. Neuroglia cells with large cell bodies, one to several nuclei, and branched processes are frequent. The cells may be so abundant, in cases of epidemic cerebrospinal meningitis, as to outnumber the ganglion cells.

In repair the neuroglia cells pass through the usual series of changes leading to new fibril formation. In case there is no destruction of vessels, the outcome of the process will be an accumulation of neuroglia fibrillæ which at first slowly contracts, but finally remains stationary. The fibrillæ abut endwise upon the vascular adventitia. As they approach the pia they assume two relations thereto: the majority of the fibrillæ are tangential, but a number of parallel fibrillæ touch the pia endwise, sometimes fraying out. The glioses in the lower cell layers are less regular in appearance. By irregular contractions the normal radial arrangement of the nerve cells is disturbed. An irregular disposition of glia nuclei can sometimes be noted between the fibers of the white matter.

Acute inflammation of the pia mater is almost necessarily attended with effects upon the substance nourished by the membrane. Pyemic abscesses of cerebrum and cerebellum are also frequently accompanied by pial lesions. Massive abscess is often found without pial lesion; nor is the relation by veins or lymphatics to the ear always demonstrable, even in temporal abscess with coexistent inflammation of the middle ear.

Pyemic abscesses are often hemorrhagic, although lesions in the blood vessels are not always demonstrable. The hemorrhages appear to originate often in the neighborhood of the layer of large pyramidal cells.

Infection.

The central nervous system under normal conditions appears at no point to come in contact with fluids or solids which are not natural to the subject. So also bacteria fail under natural conditions, so far as is known, to lie in contact with or to inhabit central nerve tissues. The number of infections found in central nerve tissues is accordingly far below the number found in the lung, the liver, the kidney, and rather approaches the number found in the ductless glands.

Bacteria enter the central nervous system in several ways. They are borne in by the blood stream, free, in cells, or upon fragments of tissue, and eventually *penetrate the endothelium.* They are swept or grow along *lymph passages about vessels and nerves.* They spread from *neighboring lesions* by destruction of intervening tissues. They are thrust in by *wounds.*

Upon reaching the tissue spaces of the central nerve substance, they die and produce no lesion, or else grow to form local lesions, or are transmitted by blood or lymph paths to form distant lesions. There is no proof that bacteria may be transmitted from point to point through the tissue spaces of the uninjured central nerve substance; there is, however, no proof to the contrary. The local lesions due to bacteria are found at the outset in the gray matter as a rule, but readily extend into the medullary parts.

Bacterial invasion of the central nervous system fills but a small space in the scheme of nervous diseases. Multiple small abscesses and infective infarcts following pneumonia and acute endocarditis demonstrate the method by blood infection. Meningitis, brain abscess, and encephalitis following otitis media and panophthalmia illustrate direct or lymphatic extension. Meningitis is also brought about by the meningococcus, which reaches the nervous system by a path still unknown.

Bacteria invade the nervous system and the pia mater by infective emboli (lung, heart valve, general infection), sinus-thrombosis (otitis media and interna, emissary veins), extension through lymph channels (nose, sheath of optic nerve, perivascular sheaths), and direct extension (dura mater and cranium). The animal parasites (cysticercus cellulosæ, echinococcus hydatidosus) are found in lymph spaces or in the ventricles.

NEW GROWTHS.

Besides secondary tumors, of which the brain is a somewhat rare site (from *breast cancer*, *malignant chorio-epithelioma*, *melanotic sarcoma*), the nervous system exhibits characteristic primary tumors. The most frequent primary tumor is the GLIOMA which may be soft and cellular (*glioma molle*), hard and rich in fibrillary intercellular substance (*glioma durum*), or supplied with cysts and ependyma-like collections of cells (*ependymal glioma*). Multinucleated cells and cells roughly resembling ganglion cells occur in many examples of glioma. It is not clear that these types are genetically separate, although some writers have described a *glioma gangliocellulare.*

The gliomata of the brain are, as a rule, single, grow by infiltration in nerve tissues (sparing both membranes and cranium), and tend to interstitial hemorrhage and necrosis. There is no evidence that the glioma produces a toxine.

The malignancy of ordinary gliomata depends upon their intracranial situation. Just as proliferating neuroglia tissue fails to encroach seriously upon non-nervous tissues in the course of repair, so also the cells of neuroglia tumors fail as a rule to extend into non-nervous tissues and confine their infiltration to nerve tissues.

Nevertheless, gliomata will sometimes grow very rapidly into spaces offering no obstruction to their growth, as through trephine holes or into the ventricles. A glioma arising in the region of the pituitary body has been observed to erode bone, just as an aneurysm might.

An occasional glioma exhibits more active powers of invasion, resembling in some degree those of sarcoma. The fibrils and even dividing cells in such a glioma exhibit a capacity for penetrating the clefts of the pia mater, so that a glioma of one frontal lobe may grow through the pia mater into the opposite frontal lobe.

In other cases the glioma exhibits a positive preference for growing along the pial tissues, resembling in all ways a sarcoma except for the neuroglia character of the intercellular substance produced.

The logical maximum of malignancy is presented by tumors which not only invade but also produce metastases. This capacity has been observed in a unique example by Mallory, who has described a SUBCUTANEOUS GLIOMA over the coccyx, WITH METASTASES in both groins.

Very large tumors develop, often without symptoms, from the dura mater (ENDOTHELIOMATA), grow by expansion inwards, shelling out smoothly from deep spheroidal pockets in the cortex. These tumors are occasionally as big as oranges, but produce far fewer symptoms and less disturbance of intracranial pressure than the gliomata, since their growth is gradual. Tumors of this type are found for some reason often near the superficial origin of the acoustic nerve. The tumors often contain considerable masses of lime and constitute the most frequent variety of psammoma.

SARCOMATA of the brain (excepting those developed from membranes or cranium) are rarer than has been supposed. The older accounts, in which no study was made of the intercellular substances, form no good basis of statistics. Tumors of the fibrosarcoma group are the commonest variety of sarcoma found.

CHOLESTEATOMATA (pearl tumors) are epidermoid tumors, as a rule in close relation with the pia mater or the choroid plexus.

They are composed of dead and dying epithelial cells, which are often mixed with cholesterin crystals and accumulate indefinitely. The tumors are dangerous from their site.

The PSAMMOMA (tumor containing lime concretions) is a frequent tumor of the choroid plexus, and occurs also in the brain substance and in the pineal body. Microscopic examination is required to tell whether a psammoma belongs to the sarcomata or the gliomata.

Other primary tumors occur. The most prominent of these are angiomata of several types.

The CHORDOMA is a small tumor which develops from the remains of the chorda dorsalis at the spheno-occipital synchondrosis. The tumor lies at first outside the dura, but later may push its way beneath and attain the size of a cherry. The tumor is mucoid in consistence. There is a homogeneous intercellular substance. The cells are highly vacuolated.

NEUROFIBROMATA are fibrous tumors developing from the interstitial tissue of peripheral nerves. Sometimes the new growth takes place from the endoneurium, in which case the nerve fibers run separately through the tumor. Sometimes the perineurium is the starting-point of the growth, in which case the nerve bundle runs through the middle of the tumor. In the larger tumors nerves may no longer be demonstrable. The size of the new growth is not in proportion to the size of the nerve bundle from which it develops. Similar tumors may develop from other structures than nerves.

The spinal cord shows various tumors of the types seen in the brain. The condition known as SYRINGOMYELIA may be grouped with the new growths or with the maldevelopments. In syringomyelia fusiform cavities are found, as a rule in the cervical cord, related with the central gray substance, often of the posterior horns. The cavities are lined with edematous neuroglia and are thus contrasted with the cavities lined with ependyma found in hydromyelia (a dilatation of the central canal analogous to internal hydrocephalus). The origin of syringomyelia is unknown, but probably manifold. Certain cases yield typical clinical pictures.

On account of the number of tissues which go to make up or may be included in the nervous system, few diagnoses of primary tumors can be rendered without resort to methods for demonstrating intercellular substances as well as the cell forms.

REPAIR AND REGENERATION.

The peripheral nervous system exhibits remarkable reparative and regenerative processes after injury. The processes of degeneration following injury are the same as those exhibited by the central nervous system. Thus, besides the local degeneration due to trauma, a characteristic secondary degeneration affects the axis cylinders and myelin sheaths for their total length distal to the injury. This secondary or paralytic degeneration affects also the central stump as far at least as the first nodes of Ranvier above the point of lesion. The sequel to the secondary degeneration of peripheral nerves, however, differs notably from the slow gliosis which follows secondary degeneration in the central tracts. The peripheral nerves after injury tend to regain function by complete regeneration of their axis cylinders and myelin sheaths. Anatomically the peripheral nerves differ from central nerve bundles in a lack of supportive neuroglia and in the presence of the sheaths of Schwann.

It is not clear what brings about the regeneration of the conducting elements; it is doubtful whether the axis cylinders simply repeat in regeneration the course of embryonic growth by growing outward from the point of lesion, or whether they are laid down peripherally by the aid of adjacent elements.

Active proliferation of the cells of the sheaths of Schwann is shown as early as the fourth day after injury, at a time when the fragmentation of axones and myelin is still marked. The regeneration of the axis cylinders follows slowly. The regeneration begins centrally, and, where growth is not obstructed, proceeds roughly at a rate of one millimeter a day toward the periphery. This direction of growth repeats the embryonic direction, but no similar regeneration takes place into the spinal cord after resection of dorsal roots adjacent to the cord. Peripheral regeneration is favored by the presence of the corresponding motor and sensory cells. The autogenous regeneration of axis cylinders described as occurring in young vertebrates independently of the correspondent nerve cells yields a partial, but never permanent, restoration of function. A regeneration of peripheral nerves, in every sense complete, is effected by a distal new growth of axones and myelin sheaths which is earliest demonstrable in areas nearest the lesion. The axis cylinders of the central stump tend in growing out to split into bunches of smaller fibers. The rate of regeneration depends largely upon the initial character of the traumatic changes. The distance to be travelled by the axone fibrils and the varying density of the cicatrix make it impossible to assign the time of recovery within months. The most convenient tubular path seems to be chosen by the regenerating axones which grow along threads or through hollow objects inserted in the tissue. This tendency is turned to account in the surgical suturing of nerves, wherein reversed segments of the nerve itself are employed to effect union over wide gaps. After amputation curious painful tumors (" amputation neuromata ") are occasionally produced by irregular and ineffectual regeneration of axis cylinders within the scar.

In the healing of nerves there is (1) a local scar formation following the traumatic degeneration, and (2) a neurotization of the scar by distally-growing axones, and finally (3) complete regeneration of the distal portion of the nerve. Secondary degenerations in the central nervous system, on the contrary, are healed not by axone regeneration but by gliosis.

II. STRUCTURAL DIAGNOSIS.

METHODS OF EXAMINATION.

The dura mater, pia mater, vessels, and connective tissues are examined by the methods employed for other organs. Fixation in *Zenker's fluid*, paraffin imbedding, and staining with *methylene blue and eosin* form a good method at the outset. The staining with methylene blue and eosin is supplemented by the *aniline blue connective tissue* stain (Mallory). Arteriosclerosis is so large a factor in many lesions that the *elastic tissue* stain of Weigert must frequently be used.

For the study of the neuroglia and ependyma, fixation in Zenker's fluid permits the use of the *phosphotungstic acid hematein* method (Mallory). *Weigert's stain for neuroglia* may be employed. These methods will not succeed unless the tissue has been fixed within a few hours post-mortem. Fibrin stains and the iron hematoxylin method may be employed. The study of the cell bodies of neuroglia cells is best carried on in sections stained with methylene blue and eosin.

The study of the nerve cells may be adequately made with sections stained with methylene blue and eosin after fixation in Zenker's fluid. Excellent work is done with the classical *method of Nissl* (alcohol fixation, staining with methylene-blue-soap solution), and, for work on nerve cells which depends for interpretation on comparative studies in the literature, Nissl's method should be used. The manifold methods used by histologists in making clear the structure of the nerve cell are unfortunately of little avail in pathological work, as their results are too precarious or require perfect fixation or are by their nature capricious. The Golgi method, for example, yields few usable data in neuropathology.

Work upon the adnexa of the nerve cell will, as a rule, require fixation in *formalin*. The data of fatty degeneration are gotten by the *Marchi method*. The presence or absence of the myelin sheath is determined by *Weigert's method for myelin*. The axis cylinder and its fibrillæ are as yet scarcely accessible to extensive pathological work. The presence of axis cylinders can be made out by the use of several of the methods mentioned above.

The methods employed fall into two classes according to the desire of the worker to study — on the one hand the *cause* and nature of the lesions, on the other hand the extent of their *effects*. It is the effects in tract degeneration which, as a rule, engage neuropathological attention.

INTERPRETATION OF GROSS APPEARANCES.

It is difficult to interpret the gross appearances of the nervous system in disease. The visible and tangible data in the *peripheral nervous system* are confined to solutions of continuity, frank atrophy, interstitial neuritis, and involvements by extension from other lesions; many of the most essential changes escape detection. The data of muscular atrophy and apparent hypertrophy should be considered amongst peripheral data.

Certain gross data of the *central nervous system* permit *immediate interpretation*. Thus the solutions of continuity in the brain and cord, voluminous effects of vascular disease (sclerosis, aneurysm, hemorrhage), massive abscesses, many cases of acute and chronic meningitis, the effects of heightened intracranial pressure, edema, internal hydrocephalus, certain tumors, and various aplasias and maldevelopments permit diagnosis on inspection.

Another series of data becomes clear when *considered* together *with findings elsewhere* in the body; thus metastatic tumors, the results of pyogenic and other infections, tubercles, gummata.

There is a great residuum of cases in which the *diagnosis* must be left *in doubt from gross findings.* As an example may be cited the diagnosis of glioma. Experience shows that little can be told from the site, size, shape, color, consistence and other gross characters of a tumor-like mass in the brain, what kind of tumor it may be, or even whether it be a tumor. Brain tumors have in the gross been confounded with tubercles, with gummata, with lesions in a stage of repair, and with areas of hemorrhage, and contrariwise. And tumors have been found microscopically where no tumor was expected from gross appearances. The gross diagnosis of glioma is often successful, but only because gliomata are common. It is, in general, hazardous to say glioma from gross appearances, and equally hazardous to say anything else in the test case.

It is hard to lay too much stress on the mistakes of diagnosis produced by the *artefacts* made in removal and inspection of the nervous system. The mistakes due to this cause extend into the region of microscopic diagnosis. The fascicular structure of many parts of the nervous system readily permits the most varied and gross translocations of tissue and *apparent heterotopiæ*, which are not interpretable in microscopic sections. Moreover, the size and heterogeneity of nerve cells make them easily accessible to apparent lesion through artificial pressure. *Post-mortem changes* are of less importance in this matter, although the data as to consistence are disturbed. Then follows a series of artefacts produced, like many in other organs, by the fixatives employed. Reliance is nowadays placed upon total immersion in a solution of formalin or upon various methods of embalming the nervous system in situ. The results and the extent of some lesions are well studied in this way. Many data concerning causes are, however, lost.

DISEASES OF DURA MATER.

The diseases of the *dura mater* are chiefly inflicted upon it from without: from the bone or from the underlying pia mater and the nerve tissue. After trauma we may get severe hemorrhage, particularly from the middle meningeal artery, which may bring about an *extradural hematoma* capable of producing tremendous compression of the nervous system. Examples of such trauma are found both in the course of the work of the obstetrician and upon the football field. The tissue of the dura itself seems to be subject to lesions chiefly upon its inner surface and here we find characteristically the *gumma* or multiple gummata, and particularly in the spinal dura the *tyromata* and tubercle-containing lesions of tuberculosis.

A quite characteristic disease, whose nature is not exactly understood, is the so-called pachymeningitis chronica interna hemorrhagica. In this disease upon the inner surface of the dura we find one or more *pseudo-membranes*, highly vascular and showing organization in various stages. The origin of these membranes is undoubtedly the rupture of vessels, but there is still doubt whether these ruptures are all traumatic or whether they are connected with the vascular disease which the old men in insane hospitals show in this condition.

Whatever the cause of the original effusion of blood, it is at any rate true that thin vessels of the organizing tissue of the membrane are apt to rupture and give rise to fresh hemorrhage, which in turn organizes and gives rise to other hemorrhages. Organizing hemorrhages do not necessarily occur upon the internal surface of the older membrane; fresh hemorrhages may be interpolated between two older membranes.

The *dura in children* is adherent to the calvarium forming apparently, in a truer sense than in the adult, an internal periosteum for the cranial bones.

Again at the other extreme of life the dura is frequently found *adherent to the calvarium*, notably to the frontal and parietal bones, and although we may dignify this condition with the name chronic internal fibrous pachymeningitis, it is still unclear to what cause we may attribute the fibrous change.

We may perhaps assign this fibrous change of the dura to the limbo of chronic conditions, resembling milk patches of the heart, the chronic fibrous thickenings in the peritoneum, shown, for instance, in the "iced liver" and the "iced spleen," and the slight chronic changes in the pleura, whose bacterial origin still rests in doubt.

In old age, along with tremendous thickening of the cranial bones, particularly of the frontal bones, the dura may become quite absorbed and the eburnated smoothly nodular surface of the thickened bone may be in close apposition to the pia mater. In very few conditions is the dura mater adherent to the pia mater.

The *Pacchionian granulations* (arachnoidal villi), whose frequency along the lips of the longitudinal fissure in adult life is so great as to warrant our terming them "normal," are received into the pockets of the dura mater, and these structures are occasionally quite interadherent. If, however, one should find an extensive adhesion of the dura to the pia anywhere over the flanks of the brain, one would be almost warranted in thinking of syphilis as the probable agent. Such adhesions are rare unless we are dealing with syphilis, tuberculosis, or tumor of the underlying regions.

There is a rare condition known as *multiple cerebral hernia*, in which small masses of nerve-cell-containing tissues are found lodged in small narrow necked cavities in the dura mater, rarely over a centimeter in thickness. The stratification of the nerve tissue in these small herniæ is only roughly preserved and the nerve cells may undergo calcification.

DISEASES OF PIA MATER.

The pathology of the dura mater dealt largely with conditions imported from without, with diseases which might be termed exogenous with respect to the pachymeninges.

In the case of the pathology of the pia mater, on the contrary, we begin to deal with diseases which are in a truer sense entities. The leptomeningitides, whether acute, subacute or chronic, whether traumatic, bacterial or toxic, or of obscure origin, form a group of diseases of the greatest possible consequence in neuropathology. The pia mater is more than a mere trabeculation in the architecture of the nervous system. The pia mater is essentially the nutrient membrane of the nervous system.

It becomes difficult in working upon the pia mater not to work also upon the underlying structures, and a systematic separation of the pathology of the pia mater from the pathology of the subpial layer of neuroglia is scarcely desirable.

The thickness, texture, and closeness of attachment of the pia mater should be noted. Judgments of thickness in sections must be modified with the direction of the section, as planes tangential to the cortex cut broader areas of pia. Thickening is usually best marked in the outer layers of the pia. The cells of exudations resemble those elsewhere, save that *pigment-bearing or cell-containing phagocytes occur very early in large numbers.* The phagocytes accumulate in lesions of the most varied origin. Mitoses in endothelial cells are found. The forms known as compound granule cells are frequent, containing various products of degeneration of cell, fiber, and myelin.

In acute lesions the amount of edema and fibrin varies greatly. The amount of edema of the pia depends somewhat on the degree of internal hydrocephalus. There is considerable *fibrin in exudates due to the meningococcus and the pneumococcus.* The *intima of the arteries shows proliferative changes* in syphilitic, tuberculous, streptococcal, and pneumococcal meningitis, more rarely in other forms.

In chronic lesions (as healing meningitides due to the meningococcus or the ordinary pyogens) the collections of *lymphoid and plasma cells* about the vessels, especially about the veins, become prominent. These collections are characteristic only in combination with other lesions, such as *tubercles*, *gummata*, and the destructive nerve cell changes and proliferative glia changes in *general paresis of the insane.* About the smaller vessels in the cortex it is noteworthy that the plasma cells readily assume a flattened shape.

Many hardening fluids cause apparent dilatation of perivascular spaces, resembling similar spaces about nerve cells.

NEUROGLIA AND EPENDYMA.

The cells of the supportive neuroglia have round or oval nuclei according to their situation among loose or stratified fibrillæ. The cell bodies are scarcely evident either in normal supportive neuroglia or in the overgrown neuroglia in a reparative or compensatory lesion (lining of old cyst of softening, posterior columns in advanced tabes dorsalis). In stains for intercellular substance (Weigert's or Mallory's neuroglia stains, Mallory's aniline blue connective tissue, iron hematoxylin) the fibrillæ are shown to be everywhere free from the cells (which appear as free nuclei) crossed and recrossed by separate fascicles of straight or smoothly curving fibrillæ, each of one diameter throughout. The number of fibrillæ to a cell is indefinite; it is usually impossible to say whether or not a fibrilla belongs to a given cell. The number of fibrillæ, and to a certain degree the number of corresponding nuclei, is normally greater in the sulci than over the surfaces of the gyri. In the subpial layer of the cortex cerebri it is difficult to estimate the thickness of neuroglia to be termed a lesion. False estimates based on sections made through shallow sectors of cortex must be avoided. There is an increase of thickness of the subpial glia with advancing age.

Where the neuroglia is still actively growing the cell bodies are visible. The nuclei may be larger and clearer, and are, as a rule, eccentrically placed in the cell. Two or more nuclei are not seldom found in a cell. Where the fibrillary intercellular substance is not too dense, the cell bodies may be seen to have processes, so that the cells roughly resemble ganglion cells. The cell bodies are, however, homogeneous and contain no granules. The cell processes are often branched and end bluntly. Along their edges may occasionally be seen fibrillæ which are apparently in the act of separating from the cell. It is such cells which, from their appearance in Golgi impregnations, have been termed spider cells.

In the nerve cell layers the neuroglia cells are rarely found increased without corresponding changes in the nerve cells. Sometimes in the cortex in general paresis the neuroglia cells far outnumber the nerve cells. The age of foci of gliosis can be roughly told from the presence, in acute lesions, of mitotic figures, multinucleate cells, and cells with branching processes; in later lesions of cells, with fibrillæ apparently in the act of splitting off from processes, and cells with smaller cell bodies in whose neighborhood the fibrillæ outnumber the processes, and, finally, of fascicles of fibrillæ in which relatively few, apparently free nuclei are imbedded. The mitoses of endothelial cells, so frequently found in destructive brain lesions which are still active, may sometimes be confounded with true neuroglia mitoses. In the pineal body, in places where the neuroglia abuts upon non-nervous tissue (adventitial and pial connective tissues), in gliomata, at the edges of old cysts of softening, and occasionally elsewhere, much larger and strap-shaped fibrillæ are found. In appropriate places these fibrillary masses may be shown to fray out at the ends like cut wire rope. Some of the structures described as neuroglia feet applied to vessels can be resolved into such structures.

The ependyma is often desquamated, especially from the tops of the elevations in granular ependymitis and in edema of the ventricular walls. Over areas from which the ependymal layer has been absent for some time there occur focal fibrillary overgrowths of neuroglia. With advancing hydrocephalus these focal accumulations of cells and fibrillæ condense and are projected farther and farther beyond the ependyma layer to form the grossly evident granules of granular ependymitis. This condition is perhaps wholly a mechanical effect. It occurs in arteriosclerosis, cardiac, and cardiorenal diseases, as well as in tuberculous meningitis and local brain diseases with increase of ventricular fluid. It is characteristic in general paresis of the insane.

Below the ependyma there occur in many diseases, but especially in epidemic cerebrospinal meningitis and in tuberculous meningitis, characteristic multinucleate structures, in whose cytoplasm may be light areas containing numerous dots or short rods which assume the neuroglia stain. Similar structures are seen in the neighborhood of the central canal of the cord, and here numerous fibrillæ run in close apposition to the cell walls.

MALDEVELOPMENT.

Wide variations in the contour and complication of the gyri are still normal. Cerebral hemispheres differ widely in the development of fissurets and annectent gyri. From these slighter deviations from the mean, it is not possible to induce anything with respect to mental or other capacities of the subject.

Well-marked asymmetries, approximations to the smooth brains of the lower animals (MACROGYRIA), and undue richness of convolutions (MICROGYRIA) occur both generally and focally.

Of the changes in shape through loss or absence of parts, one of the most characteristic is PORENCEPHALY, a condition of local funnel-shaped defect, often in the central gyri of a hemisphere, of which many degrees occur up to complete fenestration of the lateral ventricle. Porencephaly and kindred defects and local atrophies follow obstetrical and other injuries, with or without infectious complications, or may be the effect of thrombosis, embolism, or vascular changes, with incomplete repair.

There is a large series of characteristic alterations in shape of developmental or intra-uterine origin. The cases of AGENESIA of the nervous system range as a rule from the higher more inclusively to the lower mechanisms. The agenesia may consist in almost complete absence of coördinating mechanisms, seen in the MONSTERS.

Gross malformations of the nervous system are largely related to defective development in the posterior median line. The neural groove may fail to form the neural canal altogether (CRANIORRHACHISCHISIS), above (ACRANIA), below (RACHISCHISIS).

Acrania may or may not coexist with absence of brain (ANENCEPHALUS).

Cases of agenesia are theoretically distinguishable from cases of APLASIA. In aplasia there is no defect in the laying down of the original tissues in embryonic development, but there is a defect in the growth from the original tissues, the deficiency in growth is not always complete, and various degrees of HYPOPLASIA may be distinguished.

There is a remarkable condition of CYSTIC APLASIA found in the cerebral hemispheres. In this condition the ground plan of the cerebrum is preserved, and the system of ventricles is intact. But the space normally occupied by gray and white matter is a cystic space, trabeculated by lace-like vessels running in from the intact pia mater. The pia mater itself is of a normal character, save that it is almost devoid of sulcal markings. The dura mater and the skull are also of a normal appearance. The explanation of cystic aplasia is facilitated by microscopic examination of the lace-like trabeculæ which run from the pia mater to the subependymal region of the intact ventricles. These trabeculæ are composed of vessels surrounded by neuroglia tissue; but the neuroglia tissue is in turn found to be surrounded by connective tissue of the mesoblastic type. It is probable that the cystic chambers in the cerebrum are in part due to the dilatation of perivascular spaces, with eventual rending apart of their walls, as the brain plan continues to enlarge, and the neuroglia masses contract. The original injury is probably small and just severe enough to destroy the nerve cells (or neuroblasts) and leave the neuroglia-cell series intact. The failure of cell-processes and whole fiber systems (the pyramidal tracts) to develop coördinately with the expansion of the brain envelopes has increased the ultimate loss of tissue many fold.

The lesser grades of agenesia and aplasia exhibit maldevelopment of the higher (phylogenetically newer) mechanisms, so that the brains more or less approximate those of the lower orders of vertebrates.

The brain may be represented by a mass of the usual shape, but unduly small (MICRENCEPHALIA). Or the brain substance may be thinly spread over dilated ventricles which may contain several liters of fluid (CONGENITAL INTERNAL HYDROCEPHALUS). The cranium may be in part absent, permitting the brain and its membranes or the membranes alone to herniate (ENCEPHALOCELE, MENINGOCELE).

A similar series of malformations occur in the spinal system, where through rachischisis a number of structures are permitted to herniate and form voluminous skin-covered swellings (SPINA BIFIDA). HYDROMYELIA is a dilatation of the spinal central canal, the analogue of internal hydrocephalus above. If the cord lies in its usual place, there may take place a dilatation and thinning of its posterior wall with hernia through the defective lumbosacral arches (SYRINGOMYELOCELE). Much more commonly the intact cord is carried posteriorly across the hernial sac to be attached to the wall of the cyst, which becomes dimpled or biscuit-shaped thereby (MYELOCELE). If the central canal of such a translocated cord becomes dilated, hydromyelocele (MYELOCYSTOCELE) ensues. It is plain that surgical interference may be dangerous where cord substance lies immediately beneath the skin, but that a simple meningocele or dilated and herniating arachnoid membrane may be more favorable for operation.

Dimples, sinuses containing hairs (PILONIDAL SINUSES), and cysts may develop in the median line above the anus from remnants of the posterior end of the neural groove. These structures have no relation with the spinal canal, which is, as a rule, perfectly developed.

Ill-developed brains differ from brains which have been subject to lesion by the absence of scar tissue and gliosis. Nevertheless the injuries may be wrought so early in life that well-marked gliosis is not yet possible. In such cases, for instance in porencephaly, it may be impossible to distinguish from an examination of the cells whether the lesion is the effect of maldevelopment or early lesion. The brains of old idiots form the most fruitful material for study of these conditions. It is sometimes possible in these brains to secure fair imitations of the cortex of lower animals. The cellular structure of the human fetal brain of various stages is reproduced in some cases.

Another series of maldevelopment cases shows not merely absence of parts and stoppage of cell development, but actual distortions and heterotopia of structures. An instance of this is the formation in malformations of the cerebellum of islands of cells resembling Purkinje cells, but without processes, surrounded by a few cells resembling those of the granular layer.

FOCAL LESIONS.

The massive abscesses, derived by extension from the middle and internal ear and found in the temporal lobe and the cerebellum, are unmistakable. They are usually due to the pneumococcus, and are often of long standing and encapsulated. The foci of greatest destruction seem often to occur in the little-nourished area of the white matter of the temporal lobe between the termini of the cortical and the ganglionic arterial systems.

No other massive lesions are as a rule confused with otitic abscess. Large solitary tubercles and gummata require microscopic diagnosis. The findings in other organs are important here.

More characteristic are the miliary tubercles found in disseminated tuberculosis, either separately or in the fibrino-purulent exudate at the base of the brain. The miliary and conglomerate tubercles are often found on the Sylvian arteries, in the choroid plexus, and on the cerebellum, but more sparingly in the vertex. The gross differentiation between tuberculous and granular ependymitis is sometimes impossible.

Diffuse leptomeningitis is unmistakable. The streptococcus may be recovered from what looks like a slightly turbid edema of the pia. The fibrinopurulent type of tuberculosis meningitis may resemble, in the absence of careful search for tubercle, an acute meningitis due to the pyogens.

Leptomeningitis due to the meningococcus shows in very acute cases little exudation, except at the base; the surface of the brain is pink, the pia is edematous, and the beginnings of the exudate appear as yellowish lines along the sulcal veins. The exudate later becomes very fibrinous and is most marked as a rule at the base of the brain, in the cerebellar meninges, and near the fissures of Rolando. The spinal exudate is less in the pia than in the sabarachnoid space and is most marked posteriorly. The fluid of the ventricles is increased and cloudy; the ependyma soft, lusterless, uneven. The exudate is apt to extend along the optic, trigeminal, facial, and auditory nerves.

The lesions of the leptomeningitis due to the pneumococcus, staphylococcus pyogenes aureus, and streptococcus are rarely so extensive as the meningococcal lesions. The cord is not so extensively attacked, and the nerve roots are spared. Microscopic examination is necessary to distinguish all the forms with certainty.

Whereas massive abscess and various types of leptomeningitis are grossly striking, it may be hard to distinguish clearly the smaller lesions of acute diffuse encephalitis, meningoencephalitis, and ependymitis. The small pyogenic abscesses (ineptly likened to flea bites) may be hard to tell from perivascular hemorrhages. The larger pinkish edematous areas are often confused with areas of encephalomalacia of embolic or thrombotic origin.

The pyogenic abscesses are in fact often hemorrhagic. Bacteria (Staphylococcus pyogenes aureus, Bacillus typhosus) sometimes occasion extensive hemorrhages in the cerebral substance, which may break into the ventricles and present the picture of an apoplexy of arteriosclerotic origin.

The gross picture of chronic leptomeningitis is well defined. The vertex rarely shows more than small linear plates of thickening over sulcal veins. The tissues at the base show considerable thickening. In many cases the openings in the roof of the fourth ventricle have become occluded by scar tissue, the outcome of organization of exudate there. A frequent outcome of this occlusion, favored by chronic changes about the choroidal vessels is dilatation of the third and lateral ventricles (chronic internal hydrocephalus).

Changes in the cortex beneath the exudate in cases classified as leptomeningitis, although grossly invisible while-acute, can give rise to small adhesions which prevent the pia from stripping readily.

Similar cortical adhesions of great number and extent are found in the brains of general paresis of the insane. Earlier stages may be seen in tuberculous meningitis and in syphilitic meningitis.

Adhesion between dura and pia occurs seldom (except where normal about transarachnoidal vessels and arachnoidal villi) ; it may occur in extensive trauma, over tumors, and as a healed syphilitic lesion.

The dura mater of children is adherent to the calvarium. Old subjects often show adhesions of varying extent over the vertex opposite the bregma (chronic adhesive pachymeningitis). The dura of the cervical region of the cord is at times locally much thickened, so as to resemble a fibrous tumor; the chronic inflammation involves also the pia mater, the nerve roots, and even the cord septa (*pachymeningitis cervicalis hypertrophica*). The origin of the process is doubtful.

APPEARANCES IN ACUTE FIBER DEGENERATION.

A few hours after separation of a myelinated fiber from the cell which controls its nutrition, the myelin sheath swells and undergoes a coarse irregular subdivision into particles which tend to override one another and produce varicosities of the sheath. The particles stain with methods for staining fat (Marchi, Scharlach R.). Ten days to a fortnight after injury, the particles have undergone a fine subdivision and begin to be carried away by phagocytic cells. The phagocytosis lasts two to three weeks longer.

Parallel with the myelin sheath changes proceeds a series of changes in the axis-cylinder; swelling, hyaline change, formation of varicosities, granular change, eventually reduction to a stiff thread or complete absorption.

THE AXONAL REACTION IN NERVE CELLS.

Section of a nerve fiber, or injury thereto, reacts upon the controlling cell. The cell body swells; the Nissl bodies fail to stain (*chromatolysis*); the nucleus becomes a little smaller, stains more deeply, and assumes an eccentric position in the cell body. After several weeks, the cell either progresses to complete degeneration or undergoes restoration parallel with the regeneration of its fiber. The axonal reaction can be demonstrated only in cells possessing Nissl bodies and can be produced, *e.g.*, in the nucleus of the facial nerve upon evulsion of the nerve or in cells of the anterior horn upon cutting an anterior root. The axonal reaction has been much employed in the experimental demarcation of anatomical nuclei.

SECONDARY DEGENERATIONS.

Removal of ONE HEMISPHERE produces (1) partial degeneration of the genu, body, and splenium of the *corpus callosum*, which can be traced into the sound hemisphere. The anterior commissure is not involved. (2) The *internal capsule* degenerates on the injured side, together with the continuous fibers of the pyramidal tracts, frontopontine, and temporopontine tracts. (3) Fibers running out of the internal capsule into the *optic thalamus* degenerate, as well as (4) cells of *substantia nigra* and (5) cells of *pontine gray matter*.

Removal of the PRECENTRAL GYRUS on one side produces (1) degeneration in fibers coursing through the underlying white matter to converge into the anterior two-thirds of the posterior limb of the internal capsule. Thence the fibers run in the middle ventral portion of the foot of the cerebral peduncle (*pyramidal tract*), and for the most part decussate in the medulla. The fibers that decussate run in the crossed pyramidal tract; those that fail to decussate, in the direct pyramidal tract. (2) A limited degeneration takes place in scattered fibers of the *corpus callosum.* (3) Various long and short *association fibers* degenerate.

Removal of OCCIPITAL GYRI produces a degeneration distributed through the white matter in the *sagittal radiations* into the external geniculate body and a part of the *anterior corpus quadrigeminum* on the side of lesion. The degeneration fails to involve the optic tracts and the pulvinar. When both occipital regions are removed, the fibers of the *tapetum* and *splenium* of the corpus callosum degenerate thoroughly.

Removal of the first and second TEMPORAL GYRI produces secondary fiber degeneration as far as the *internal geniculate body*, and numerous cells of the internal geniculate body also degenerate.

Removal of the ANGULAR GYRUS produces degeneration of fibers running to the *pulvinar* and degeneration of the pulvinar cells as far as the internal geniculate body.

Removal of one FRONTAL POLE produces secondary degeneration of the inner part of the cerebral peduncle (*frontopontine tract*) and in the anterior and mesial nuclei of the *optic thalamus*.

EXAMPLES OF CEREBRAL SECONDARY DEGENERATIONS.

Cerebral Hemorrhage.

Apoplexy, or cerebral hemorrhage par excellence, is most often due to rupture from disease of a branch of the anterolateral group of the central ganglionic arterial system (branch given off frequently from left middle cerebral artery). The corticospinal motor path becomes degenerate in the cases which recover. Over and above certain general symptoms, the main result is hemiplegia of the side opposite to the hemorrhage. Considerable gradual restriction of the number of muscle groups affected is the rule. Contractures set in, as in the case of cerebral palsy of children and cerebral monoplegia, and atrophies of the correspondent limbs are equally absent. The aphasia, which complicates extensive left-sided hemorrhage, is likely slowly to disappear.

Cerebral Palsy of Children.

Extensive lesion, such as acute hemorrhagic encephalitis of the Rolandic region, produces, as a rule in children, convulsions followed by a hemiplegia or unilateral paralysis of the arm and leg, or the arm, leg, face and possibly the tongue. Stable contractures or spastic innervation (tendency to tonic contractions in lieu of movement) of the muscles follow. Characteristically also occur associated movements, athetosis (slow, successive contractions of muscle groups, with extension and flexion, adduction and abduction, at short intervals), a degree of imbecility, and a tendency to convulsions on the paralyzed side.

At autopsy the corticospinal motor tract will be found degenerated. At successive levels this tract occupies, first, a part of the converging coronary or tegmental radiations of the centrum semiovale, next, the anterior two-thirds of the posterior limb of the internal capsule, and, now as the pyramidal tract, the middle ventral portion of the foot of the cerebral peduncle. In its course through the pons and medulla oblongata, the various bundles corresponding with the cranial nerves diverge to the raphe, decussate, and come into relation with their respective cranial nerve nuclei. The fibers of the corticospinal tract itself continue to the (incomplete) decussation in the medulla. The degeneration in the spinal cord will then be seen in large part in the pyramidal tract of the opposite side, but in small part also in the direct pyramidal tract.

Cerebral Monoplegia and Cortical Epilepsy.

Under the head "cerebral palsy of children," the frequent cause mentioned was hemorrhagic encephalitis. A similar hemiplegia due to cortical lesion fails to occur in the adult. In the adult inflammatory lesions of the cortex are likely to be so extensive as to produce more general signs than hemiplegia; or, if small, experience shows that the signs produced are of limited range. A destructive lesion of the motor cortex produces some form of cerebral monoplegia or paralysis (without atrophy) with contracture and increased deep reflexes of the limb or muscle groups involved. If the lesion be not destructive, but leave the gray center in a state wherein its functions are performed abnormally, a local form of epilepsy (cortical or Jacksonian epilepsy) is produced, characterized by unilateral spasms (bilateral in the case of muscle groups which normally act bilaterally).

Just as in the cerebral palsy of children, a variety of lesions may produce in the adult the local signs of cerebral monoplegia or cortical epilepsy; but in the latter, perhaps the most frequent cause is new growth, though trauma and inflammatory lesions are often found.

In the case of cerebral monoplegia the degenerate tracts may be followed down in the corticospinal tract sketched under cerebral palsy of children. The coronal radiations from the cortex are slowly shifted in their downward course, so that in the cerebral peduncle the fibers from the frontal cortex come to lie internally and the temporal and occipital fibers come to lie externally with the motor or pyramidal tracts set between.

CEREBELLAR LESIONS.

Removal of one CEREBELLAR HEMISPHERE leads to degeneration of all three processes. (1) The degeneration of the *brachium conjunctivum*, to be complete, requires total destruction of the dentate nucleus. (2) The degeneration of the *pontine fibers* is connected with cell degenerations in the ventral part of the gray matter of the pons on the side opposite to the lesion. (3) The degeneration of the *corpus restiforme* is connected with cell-degenerations in the nucleus of the restiform body, in the *inferior olive of the opposite side*, in the lateral column nucleus, and in the direct cerebellar tract together with the cells of Clarke's column.

The cerebellum is an organ the greater part of which remains obscure in function. It is an apparatus which, by means of its connections with the cerebrum and with the cord, together with the interconnection of its parts by virtue of the pons, is best situated in the central nervous system to throw impressions from the sensory apparatus into connection with the motor and regulatory apparatus. The cerebellum receives impressions from at least three different sources, from the cerebrum, from the back and neck by virtue of fibers from Clarke's column, and from the vestibular portion of the eighth nerve. Besides these sources of impulse it also receives impulses from the olivary apparatus which is interposed between the cord and the thalamus. Of course the cerebral connections of the cerebellum are lacking in the lower vertebrates. Moreover, the connections with the olivary apparatus are developed only gradually as we rise in the scale to the mammals. The fundamental mechanism of the cerebellum is consequently largely related with its connections with the trunk and the nerves of the equilibration apparatus.

Of the paths leading out of the cerebellum one of the most important leads to the nuclei governing eye movements. These paths go by way of the dorsal longitudinal bundles, which by means of their descending portions throw the cerebellum, the eyes, and the trunk together in a single related apparatus. There is another direct path to the spinal cord so that irritation of the vermis of the cerebellum not only produces deviation of the eyes toward the irritated side, but also may bring about back and limb movements on the same side. We do not yet understand the function of the olivary apparatus. The olivary apparatus, like the cerebral connection of the cerebellum, arrives late in the animal series. If the loss of cerebellar tissue has occurred early enough in life it is possible to compensate for most of its functions. Subjects with congenital defects of the cerebellum may consequently show few disturbances and these may be gradually done away with in the rest of life. The cerebellum was originally an apparatus concerned with the static relations of the body. The cerebellum begins to be complicated with the swimming reptiles. The better a fish can swim the more complex its cerebellum.

If we take away one hemisphere of the cerebellum then we get all kinds of pareses and spasms in the muscles of the body. The movements become so ataxic that the animal cannot eat, but all this is gradually compensated for, and only an intention-tremor may remain. In case we take away both hemispheres with the vermis then the results are not so severe, although in principle the same, and all these muscular disorders may clear up with the exception of the intention-tremor. The significance of the cerebellum may consequently be summed up as follows: All the sensations and impulses which the muscles, joints, and tendons receive from the outer world are transferred to the cerebellum. The sensations from the static or equilibration apparatus in the labyrinth are also transferred to the cerebellum. In the cerebellar apparatus the regulation of muscular tone and the finer movements of the muscles is performed. Moreover, the eye movements which are so important in equilibration are also regulated from the cerebellum. Probably all these regulations relate to the muscles upon the same side of the body. One cerebellar hemisphere has to do with the muscles on its side and only to a slight degree with the muscles of the opposite side of the body. The cerebrum and the thalamus exert action upon an apparatus which is already capable of performing much of its function independently. The cerebellum furthermore controls positions and gait by means of its relations with muscular tone and with the coördination of muscles of the neck and trunk. The symptoms of cerebellar disease are still relatively obscure. This obscurity is partially accounted for by compensatory function of numerous other portions of the central nervous apparatus. Disease of the vermis, particularly of its posterior portions, produces cerebellar ataxia, disorders of the position of the eyes and of the position of the head. Animal experiments indicate that weakness of muscular tone should follow. Vertigo is a frequent symptom early and late. As to the tremor which accompanies these diseases, we are not yet sure whether it is a focal symptom of the disease of the cerebellum or a symptom related with disease of the neighboring apparatus. The same holds of ataxic speech disorder.

DISEASES OF THE PONS AND BULB.

Glossopharyngolabial (bulbar) paralysis is a name given to several types of disease (the so-called progressive form of beyond middle age, a hereditary form found in children, an acute apoplectic form, a compression type from new growths). It is obvious that small lesions of various nuclei will produce appropriate loss of function and degeneration in appertaining tracts. In the bulb the tracts and the centers are collected into very small compass, so that a lesion the size of a pea may cause bilateral paralysis of, for example, the twelfth nerves. A lesion placed beside the pyramidal decussation produces crossed hemiplegia, involving the fibers of the motor tracts of one side above the decussation and tracts of the other side below the decussation. Contralateral hemiplegia ensues upon lesion above the decussation just as in cerebral palsy of children or in the classical cerebral hemorrhage; but inasmuch as the destructive lesions must be much smaller so to single out limbs or muscle groups, the history and clinical pictures are likely to be different. These local pontine and bulbar diseases are apt to be chronic. An exception is the form clinically known as the acute apoplectic form due to basilar thrombosis or to encephalitis (acute polio-encephalitis inferior). Acute hemorrhagic encephalitis confined to the central gray of the floor of the third ventricle and the Sylvian aqueduct (acute hemorrhagic polio-encephalitis superior of Wernicke) produces a bilateral ophthalmoplegia, termed nuclear, with correspondent secondary degenerations in the oculomotor paths in chronic cases.

TRANSVERSE LESIONS OF THE SPINAL CORD.

Transverse lesions of the spinal cord produce pictures of degeneration which differ somewhat at various levels, but have several features in common. Thus, near the plane of lesion, total degeneration of ascending, descending, and commissural tracts is found. At various levels remote from the transverse lesion the tracts degenerate according to a general principle, viz., the motor conducting paths *in general* degenerate downward, the sensory paths *in general* upward.

Below the plane of lesion the pyramidal tracts degenerate, as in the series of lesions just described (cerebral palsy, hemorrhage into internal capsule). In transverse lesions of the upper cord both the crossed and the direct pyramidal tracts degenerate below the plane of lesion. But, inasmuch as the direct pyramidal fibers have all decussated by the middle or lower thoracic segments, below that level the descending degeneration is confined to the crossed pyramidal tract.

Above the plane of lesion (1) a portion of the fibers of the posterior columns degenerate, but, on account of fresh accessions of uncut fibers from higher posterior roots, the area of ascending degeneration continually shifts inward, occupying the column of Goll. (2) The direct cerebellar tracts are degenerated in transverse lesions of the cord which are high enough to cut off the connections between this tract and the cells of Clarke's gray column, which is developed in the median gray of the thoracic cord. But in transverse lumbar lesions the direct cerebellar tract is naturally at no point degenerate.

Of the other tracts of the cord a variety of interesting facts is known. The degenerations of the short and commissural tracts near the lesion are obvious, but not extensive. The degenerations in the long tracts other than those described are difficult to estimate, and particularly difficult to translate into functional terms because the fascicles are composed of a mixture of fibers, some of which are ascending and others descending. The posterior columns show, besides the extensive degeneration above the plane of lesion, also small (in cross-sections comma-shaped) tracts of degeneration below the plane of lesion. The fibers concerned in this descending degeneration are the descending branches of the dorsal root fibers.

UNILATERAL LESIONS OF THE SPINAL CORD.

Stab wounds occasionally produce hemisection of the spinal cord, upon which follows the symptom complex known as Brown-Séquard's paralysis. The anatomical basis of this symptom complex is in part obscure. Paralysis on the side of the lesion is due to section of the direct pyramidal tract. Anesthesia on the side opposite to the lesion is supposed to be due to the section of sensory fibers which decussate immediately after entrance into the cord. But the anesthesia is incomplete, as the muscle sense is intact; accordingly the fibers corresponding with muscle sense are supposed to decussate higher up. Complex but quite definite symptom groups are produced by lesions at various levels. It is impossible, as it would be unwise, to learn these complexes by rote. Only familiarity with the anatomy of the cord and results of experimental work permits diagnosis.

SYSTEM DISEASES.

The conditions sketched under secondary degeneration are the outcome of known destructive injuries. Roughly similar degenerations, in point of extent, are produced in various unknown ways. The best defined of these degenerations occur in tabes, in progressive muscular atrophy and amyotrophic lateral sclerosis, and anterior poliomyelitis. At present, however, anterior poliomyelitis may be ranged perhaps better with the results of bacterial inflammation.

Together with these conditions may be considered the combined system disease and multiple sclerosis.

Tabes Dorsalis.

A small percentage of syphilitic subjects five to fifteen years after infection, and a number of other subjects in whom syphilis cannot be proved, are attacked by a disease which early exhibits loss of knee-jerks, Argyll-Robertson pupil (accommodating for distance, but failing to respond to light), lancinating pains in various parts, analgesia usually of the lower extremities, and, perhaps, Romberg's symptom (swaying with closed eyes). Other phenomena are added later and give tabes its other name, *locomotor ataxia.* The disorder of movement is due, not to weakness, but to incoördination, and usually affects the lower extremities first. The most frequent disease of the cranial nerves is paralysis of the ocular muscles (the only true motor symptom of tabes). The optic nerves often undergo progressive atrophy. Characteristic are disturbances of the joints and bones, malum perforans (perforating ulcer, as a rule, of the sole of the foot), spontaneous gangrene, and other disorders all referable to destruction of the trophic apparatus of the spinal cord.

The degeneration of tabes progressively attacks various regions of the spinal cord. The degeneration is confined to the intradural portion of the peripheral sensory neurone, *i.e.*, the peripheral sensory nerve, the root ganglion and the extradural part of the posterior root are mainly spared. The initial sclerosis may be quite invisible to the naked eye, as the change is quite narrowly confined to the region of the dorsal root zones of the middle or lower lumbar segments of the cord. The disease is not easily recognized from the gross cord till later stages, in which a flattening and narrowing of the posterior columns of many lumbar and thoracic segments is observed. But in the middle stages it is still possible to make out an increase of consistence and a slight graying-out of the posterior columns examined in cross-section. The stage of the disease is more surely determined by microscopic examination of various cord levels. The older the process locally, the more marked the atrophy and the corresponding gliosis and the smaller the area of degeneration as seen in cross-section. The more advanced the disease, as a whole, the more entering dorsal root fibers are affected, and the wider will be the ascending tracts of degeneration in the posterior columns. It is in this disease that the prettiest demonstrations are afforded of the relationship between the columns of Goll and of Burdach and the lower and higher dorsal root systems respectively. Thus in an early case of tabes dorsalis an examination of serial sections from below upward exhibits the ascending prism of degenerated fibers slowly translocated inward, to form the column of Goll, through the accession of fresh undegenerated fibers from higher nerve roots. In the rare cases of cervical tabes the relationship is reversed. In cervical segments from a case of tabes cervicalis, it is the fibers of the column of Burdach which are degenerate; whereas the fiber system of the column of Goll, derived from the intact roots and ganglia of the lower dorsal and lumbar regions, remains unaffected. However, in the majority of cases of tabes dorsalis, seen at autopsy, the changes are already spread over many segments, and there may usually be seen gross thinning out of the dorsal columns.

Progressive Muscular Atrophy.

Persons in middle life may become subject to a slowly developing disease, which starts with a flattening of the ball of the thumb and a deepening of the interosseous spaces in the hand. Fibrillary twitchings and gradual atrophy ensue. The atrophy overtakes various muscles of the arm and shoulder, not by continuity, but by springing from one group irregularly to another group of muscles. In the course of several years most of the arm, shoulder, and back muscles are atrophied, and the muscle groups which are spared undertake, as well as possible, the functions of the atrophic muscles. The so-called "*living skeletons*" die of intercurrent disease or are destroyed by an advance of the atrophy upon the respiratory and other muscles controlled from the bulb.

The spinal cord, at appropriate levels, shows a variety of degenerations of which the most constant is atrophy of the anterior horn cells.

Amyotrophic Lateral Sclerosis.

Men of thirty to forty years sometimes become subject to a disease consisting in paresis and contracture of the arms or of all the extremities, in which the muscles undergo atrophy. The disease is apt, later in its subacute course of eighteen months to two years, to involve also the muscles of the tongue, the face, and the pharynx. Death is likely to ensue when the pneumogastric nerve becomes affected.

Nothing is known of the cause of this disease, but the findings in the nervous system are striking. The cells of the anterior horns in the cord at levels corresponding with the muscular atrophies are reduced in number and size, perhaps overpigmented. Especially the large motor cells are affected. The cells of Clarke's column remain intact. The nerve fibers of the anterior horns, the anterior root, and of the direct and crossed pyramidal tracts have disappeared. The area of the crossed pyramidal tract affected is, as a rule, larger than the similar area brought about by secondary degeneration. That the disease is progressive is shown by the occurrence of fresh fatty changes in other parts of the cord alongside the typical sclerotic lesions.

Analogous lesions to these are found, in the glosso-labiopharyngeal cases, in the cells of the hypoglossal, facial, motor trigeminal, and finally the pneumogastric nuclei, together with a sclerosis of the anterior pyramids. Essential changes are rarely found above the level of the pons. Thus, at a given level, both the whole of the spinomuscular motor path and the lower portion of the corresponding corticospinal motor path are affected.

COMBINED SYSTEM DISEASE.

A peculiar though varying set of symptoms sometimes occurs in pernicious anemia. The same symptoms and the same findings certainly also occur in cases which are not pernicious anemia. The beginnings of the disease have never been microscopically observed. The spinal cord simulates a combination of tabes with degeneration of the pyramidal tracts: thus the posterior columns and the direct cerebellar tract are degenerated, as well as the crossed and sometimes the direct pyramidal tracts.

The symptoms cannot be a mere combination of tabetic and spastic paretic phenomena, for some of these are contradictory. As a fact, according to the distribution and intensity of the lesion, two types of symptoms are found. In the first place, the motor weakness with increase of tonus (spastic paralysis) may be combined with various tabetic symptoms, such as ataxia, lancinating pains, Argyll-Robertson pupil. Or, in the second place, the picture may be predominantly that of tabes, with a motor weakness not found in tabes.

A disease exhibiting somewhat the same distribution of degeneration in the cord (degeneration of Goll's and Burdach's tracts, of Clarke's gray column and the direct cerebellar tract, together with degeneration of the crossed pyramidal tract), besides in certain cases atrophy of the cerebellum, is known as *hereditary ataxia* (Friedreich's disease).

SYRINGOMYELIA.

Persons in middle life may notice vesicles on the skin of the hands which fail to heal well. Slight wounds become easily produced. The small muscles of the hand atrophy; the interosseous spaces deepen; fibrillary tremors, "claw hand," and the picture of progressive muscular atrophy develop. The physician may be the first to detect a peculiar disorder of sensibility: whereas the sensations of touch, pressure, and position are intact, the sensations of pain and temperature are lost or decreased over wide areas (*dissociation of symptoms*).

The clinical picture is typical only because of the usual site of the fusiform glia-lined cavity, asymmetrically set, as a rule, a little posteriorly in the central gray of the cervical cord. A condition histologically exactly similar but of different site would produce a quite different picture. The clinical picture is as characteristic and definite as many of those in the system diseases, but the process is not a tract disease.

GENERAL PARESIS.

The brains of some subjects exhibit a characteristic set of changes: the pia mater is thickened almost diffusely and may be edematous; the convolutions are narrowed over limited but wide areas, and the sulci are flaring; small bits of the cortical substance may cling to the pia on peeling; on section the minute cortical vessels stand out prominently, notwithstanding the absence of arteriosclerosis. There is likely to be a moderate internal hydrocephalus and marked granular ependymitis. Microscopically the cortical vessels attract attention from the infiltration of their sheaths with lymphoid and many plasma cells. The neuroglia shows many phases of overgrowth. The swelling of the neuroglia cell bodies may be determined in regions where defined nerve cell changes are still absent. In many areas the nerve cells exhibit changes of many grades up to replacement. Their regular radial arrangement in the cortex is disturbed. The regular rows of neuroglia cells in the white matter are thrown into disorder by the loss of medullated fibers and the irregular contraction of the intercellular substance.

The spinal cords of some general paretic subjects show the characteristic changes of tabes: these cases are called taboparetic.

If the records of the subject be examined, it may be found that syphilis had occurred many (five to twenty) years before. The symptoms which have led to death had begun insidiously two or three years before: a change of character (*e.g.*, from grave to gay or contrariwise) with moral and intellectual impairment and loss of memory. The disease then progresses to graver impairment in which speech disturbance and paralytic attacks are prominent. The pupils show the Argyll-Robertson sign as a rule.

ACUTE ANTERIOR POLIOMYELITIS.

Acute anterior poliomyelitis is a disease characteristically found in children. Its healed results are seen in cases of infantile spinal palsy. The process, when caught early, is found to be a true inflammation of the region of the anterior horns, preferably of the cervical and lumbar enlargements of the cord.

Cases examined at various stages later in the disease show, first, fatty degeneration (Marchi), later, scleroses demonstrable by Weigert's myelin sheath method. Finally a stationary stage is reached in which a certain amount of atrophy in one or both anterior horns can be grossly demonstrated, and a reduction in number of motor cells with gliosis can be made out microscopically.

Anterior poliomyelitis in the acute stage is a phenomenon of infiltrative myelitis of a disseminated character. Foci are always found, when looked for, also in the medulla and the brain. The edema contributes in the formation of the limited foci. The interstitial changes do not depend upon cell or cell-group changes. In the medulla, in fact, the foci are as a rule outside the cell-groups. The cord constantly shows lesions outside the gray matter. The process is most extensive in the enlargements of the cord. The process in the upper lumbar and particularly in the lower dorsal cord affects Clarke's column as much as or more than the anterior horns at the same levels. The process varies with the vascular conditions and is not especially related with the central artery. The process is not embolic, or at least this cannot be concluded from the findings. The interstitial and parenchymal changes run parallel. One never finds nerve cell changes without interstitial changes, but in the medulla normal nerve cells can be found near areas of interstitial change. The nerve cell destruction is due chiefly to the interstitial changes.

The adult and infantile forms of the disease are similar. The phenomena in Landry's paralysis and in rabies are in the same pathological group. The disease is probably of lymphogenic origin, perhaps of hematogenous origin. Nobody has yet succeeded in producing by hematogenous infection any disease remotely resembling anterior poliomyelitis.

MULTIPLE DISSEMINATED SCLEROSIS.

Young adults, after acute infectious diseases and metal poisoning, or apparently spontaneously, sometimes develop a striking clinical picture: weakness and rigidity of legs, spastic paretic gait with "cerebellar" reeling, tremors attending and increasing with voluntary movements ("intention-tremor"), nystagmus (especially on looking sidewise), partial optic atrophy, "scanning" or "syllabic" speech, paroxysmal involuntary laughter, and weakening of intelligence.

The membranes in cases of multiple sclerosis are practically normal, except when the cerebral atrophy produces a moderate external hydrocephalus ex vacuo and in places where the sclerotic foci abut upon the pia, giving rise to slight adhesions. The cerebral atrophy which occurs is called a secondary atrophy and is not necessarily attended with focal changes. The cord is small also very often and is perhaps atrophic, though there is ground in some cases for supposing hypoplasia.

The islands of sclerosis which characterize the disease vary in diameter from fractions of a millimeter to several centimeters. The larger plaques are irregular and perhaps arise by confluence of smaller areas. They vary in number from a half a dozen to hundreds. They are described as gray, gray white, grayish yellow, ash gray, gray blue and on exposure to air assume a gray pink hue. The color of the areas is very characteristically gray rather than pink.

The surface of section of these islands fails to sink or project from the surrounding tissue. The consistence is as a rule increased and the tissue firm; and therefore distinguished from areas of disseminated encephalitis or myelitis.

The areas are rounded rather than irregular and in myelin sheath preparations look as if cut out with shears. The upper and lower ends of the islands are less rounded than the sides. In neuroglia preparations these sharp borders are lacking.

The areas occur wherever there is neuroglia: cortex, nerve roots, optic nerve, and constantly in both brain and cord.

The areas are not wholly capricious in situation but seem to prefer areas where there is normally more neuroglia, and are very frequently disposed in cord, medulla, and pons. There is also a predilection for the posterior columns and for the neighborhood of the posterior median septum. In the cord the areas occur preferably in the white matter, although there is an abnormal central gliosis. Contrary to Charcot's original opinion, the cortex is not spared by the lesion. The areas are composed of great areas of neuroglia fibers, some very thick, running in every direction (in the posterior columns of the cord they are as a rule longitudinal). The disease offers the maximum of fibrillary gliosis known. There is never any tendency to cyst formation in the areas.

Myelin sheath stains show the degeneration of the sheath. Marchi stains sometimes indicate an eccentric progress of the disease. On the periphery of some areas fat granules are found.

Modern work appears to uphold Charcot's opinion that the axis cylinders persist throughout the course of the process which destroys the sheath and produces the neuroglia overgrowth. The only opposing hypothesis in the field is that the axis cylinders grow down through the foci by regeneration after destruction early in the process.

The nerve cells are not affected. There are no secondary degenerations ensuing upon the lesions.

The process is generally regarded as congenital in origin, as endogenous and therefore as sharply separable from all secondary forms such as gliosis due to vascular, toxic-infectious, and reparative changes.

EPILEPSY.

Epilepsy is a disease characterized by loss of consciousness, loss of muscular control, and muscular contractions known as convulsions. The body is fixed in abnormal postures by tonic contractions, the chest stiffens, respiration ceases, the face becomes congested and livid. Thereupon remissions appear in the tonic contractions, which finally become "spread out" into clonic shock-like contractions. The subject shows a bloody froth at the lips and remains unconscious for a time after the contractions cease.

The seizure may be preceded by a warning (aura) in the shape of certain sensations, referred to some part of the body or to some special sense. These warnings as a rule quickly flow over into unconsciousness and thence into spasms. Slighter attacks (brief giddiness, local spasm, " sensations ") are termed *petit mal* as opposed to seizures with marked convulsions, *grand mal.*

Idiopathic epilepsy (*grand mal* or *petit mal* forms) is distinguished from organic epilepsy (due to focal lesions in the motor zone, commencing by sensations or clonic spasms in the related part changing to tonic spasms with loss of consciousness in intenser cases), from eclampsia or puerperal eclampsia (which seizures cease if the patient survives), and from hysteroid attacks (in which the spasms are all such as might be produced intentionally although they are unduly violent).

The tissues in cases of epilepsy exhibit no constant anatomical changes. Induration, that is, fibrillary gliosis, of the cornua ammonis is sometimes found. It is also common to find local indurations elsewhere, *e.g.*, in the motor cortex, which may be interpreted as the effect of trifling destructions occasioned by the epileptic discharge. It is impossible to draw the line between these glioses and the focal lesions (tumors, cysts of softening) which are found in cases of "organic" epilepsy. It is improbable that these latter lesions are produced by the epileptic discharge. It is certain that epileptiform convulsions are sometimes associated with focal lesions as the effects thereof. In the lower animals convulsions may arise from stimulation of the pons and medulla. It was at one time thought that the tonic spasms were due to irritation of the mesencephalon or lower structures and the clonic spasms to cerebral stimulation. It is now held that both types of contraction have their origin at the surface of the brain. The mechanism of the discharge is obscure. The assumption of local vascular spasm as epileptogenic is pure assumption.

III. NEUROPATHOLOGICAL PHYSIOLOGY.

A consideration of the structural side of neuropathology leads to the conception that the nervous system differs in no very essential respects from the other systems of the body. Not only are the nutritive mechanisms identical with those of the rest of the body, but also the nervous parenchyma itself effects no important deviation from the general rules of cellular pathology. Indeed it is by means of the latest great achievement of cellular pathology, viz., the *neurone theory*, that a union of the structural and the functional points of view has been effected for the nervous system. The search in one quarter for a cytological unit, in another quarter for a developmental unit, in another for a trophic unit, has culminated in the discovery of a unit, the *neurone*, which has some claim to be a functional unit for the nervous system, both peripheral and central.

THE NEURONE THEORY.

Waldeyer, 1891, offered the following definition of the nervous system: The nervous system is a collection of units which are anatomically and developmentally distinct. Each unit or neurone is composed of three parts, namely, of a nerve cell, a nerve fiber, and a terminal arborization. Conduction proceeds in some neurones from cell to arborization, but in other neurones from arborization to cell. Thus motor impulses are conveyed from cell to arborization, but sensory impulses, on the other hand, run one way in some instances, but in other instances go contrariwise (note, for example, the directions of impulse in the processes of the cells of the dorsal root ganglia).

Waldeyer's definition took its rise from the data of the silver impregnation methods of Golgi, and particularly from Ramón y Cajal's demonstration that the nerve cells of embryos and fetuses throw out processes which all end blindly. However, it has never been so clear that the nerve cells of the adult invariably remain anatomically distinct. Edinger and others have held that, although there must remain a doubt whether the processes are continuous or only contiguous, nevertheless the neurone must be maintained as a biologically independent unit.

The neurone theory has thus undergone various changes since its first exposition. The most frequent insistence is made upon the trophic nature of its function. An explanation seems demanded for the data of Wallerian degeneration and the invariable results of the method of Gudden. Thus, if destruction of a given gray center or section of a given nerve bundle constantly produces retrograde changes in certain remote circumscribed foci and the connecting paths, it is certainly possible to regard the cells involved as neurones, as units having a functional value and unity, whose anatomical nature may be left out of account.

Many of the tract diseases sketched above are neatly interpretable in terms of the neurone theory. Thus, the pyramidal tract may be considered to be a bundle of fibers belonging to the *corticospinal neurone system.* The corticospinal neurone system may be said to come into relation in the anterior horns with a peripheral or *spinomuscular neurone system.* Further, to take up the sensory half of the loop made by the projection system, the apparatus connecting sensory end organs with higher centers (which consists for the spinal cord of the dorsal root ganglia, the sensory peripheral nerves and the columns of Goll and Burdach) may be termed the *gangliospinal neurone system.* The central (intraspinal) tracts of the gangliospinal neurone system come into relation with new ascending neurone systems in the medulla (*bulbocentral neurone systems*), of which we suppose, on account of the rapid playing out of degeneration tracts at higher levels, there is an end-to-end series. Moreover, the direct cerebellar tract, which becomes degenerate on section of the thoracic cord, may, in conjunction with the cells of Clarke's column from which it takes its rise, be regarded as fresh neurone system, a *spinocerebellar neurone system.*

In a certain series of diseases (secondary degenerations, tabes dorsalis, anterior poliomyelitis, and so on) these neurone systems undergo changes as units. In some of the diseases our attention has been directed by this consideration to look for changes in the gray centers which might otherwise have been overlooked. It would be oversanguine to assume that actual progress in making clear the facts has been accomplished by the neurone hypothesis. In so far as it restates facts and discoveries made in most cases without its use, the hypothesis may be assigned a limited value. But the true cause of the so-called primary degeneration remains remote from us. It remains mysterious why the intradural portion of the gangliospinal neurone system is chiefly affected in tabes, why in amyotrophic lateral sclerosis and in progressive muscular atrophy (if they are separate diseases) the spinomuscular neurone and a portion of the corticospinal neurone are affected, and why the process in anterior poliomyelitis should sometimes be confined to the spinomuscular neurone system and sometimes involve also the direct cerebellar tract.

THE REFLEX ARC.

It is proper to point out, however, that a single neurone though it is a pretty example of a unit in cell physiology, possesses less importance as a unit in neurophysiology. The nervous system begets *no action with a single neurone.* Rather, it takes *two neurones* to contribute to the true neurophysiological unit, the *reflex arc.* The reflex arc, which is the first product of the division of labor in the lowest forms showing sensory and motor organs, remains the type physiological unit in the most complex forms, which show sensory and motor organs but also central organs. Anatomical data, cytological findings, the observation of coarse movements and of the finest physico-chemical processes of secretion, unite in showing that the type mechanism of the nervous system is the reflex arc. The task of neurophysiology is to describe and explain the compounding and interrelation of reflex arcs.

Of course the conception of a reflex arc has undergone a considerable change from the original simplicity of an apparatus for approaching or withdrawing movements according to nature of stimulus. At first sight it seems a strain to conceive entirely endogenous activities in the nervous system as going on in reflex arcs. Nevertheless, an impulse travelling from the occipital region to Broca's area and thence to medullary nuclei is an impulse which perfectly imitates the type of reflex act, even although nothing in the outer world is seen or spoken.

Reflex Acts.

But, just as the private activity of a single neurone begets no essentially neural action, so too the reflex arc, which is the outcome of connecting two neurones, begets only constant or constantly varying vegetative activities. Reflex arcs, taken by themselves, either work or fail to work on the all-or-nothing principle, varying in definite ways according to the strength of stimulus and the state of the arc structure at the time. Naturally these *vegetative activities of the reflex arc* are subject to extensive variations. But these variations are such that they fail to serve the important purposes of the organism in relation to its environment. The effect of a reflex arc's activity, viz., a *reflex act,* is an immediate effect of stimulating one sensitive point upon discharge of activities in some area habitually related to that stimulation. What the organism requires for the pursuit of its purposes is a combination of effects, the proper action or inhibition, namely, which ensues upon several kinds of stimulation. *The purposive or teleological organism requires definite action or inaction to follow stimulation which is plurifocal.* In every multicellular organism the stimulation of a given instant cannot fail to be plurifocal. It does not matter whether these stimuli are all exogenous, or all endogenous, or partly one and partly the other. The task of neuropathology is evidently to examine the effects of absence, alteration, and excess of stimulation in one or more foci as related to the habitual discharge-effects of such stimulation. Divergent and altered discharge-effects must likewise be considered.

In addition, therefore, to (1) the morphological and physicochemical considerations of *cellular pathology* as applied to the nervous system, and (2) the predominantly physical consideration of the *neurone units* with which neurophysiology begins, we are compelled to take up (3) the system of *reflex arc relations* as they are modified in spatial arrangement and in temporal succession. A finished neuropathology would therefore be concerned with reflex arc relations offering some resemblance to an applied solid geometry and to a dynamic physics.

The task of present-day neuropathological physiology is much more modest and seeks to lay down a few general consequences of alteration in various parts of the nervous system together with an enumeration of the more important reflex arcs and their interactions from the practical point of view.

Neurophysiology, dealing with reflex arcs, is much more concerned with their effects than their structure and feels empowered to neglect the relative merits of cells and fibers, neurones, and even of the constituent neurofibrils as units. Whatever is the ultimate visible constitution of the nerve-impulse-transmitting apparatus, the important task of neurophysiology is to mark out the configuration of the arcs employed regardless of details.

SYNAPSES.

But, although cytological and histological controversies do not at first sight enter the region of neurophysics, the English physiologists have brought out the importance of conditions inside the reflex arc structures. The loci of particular interest are at the confines of the neurones, at the *synapses*. The synapse is defined as the physical surface of separation between two neurones, and thus forms a kind of loop between the two conducting elements of any reflex arc. In the region of the synapse, moreover, impulses from other neurones may enter, so that the synapse may be regarded as a nodal point for the intercurrence of nerve impulses from several sources. These hypothetical synapses, according to Sherrington, " might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric changes, support a double electric layer, alter in shape and surface-tension with changes in difference of potential, alter in difference of potential with changes in surface-tension or in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge."

Now it is obvious that we cannot at the present day pick a probability or a combination of probabilities from the above list or an extension of the above list of physical possibilities. But it is evident that, since the synapses lie largely in gray matter, the study of cortex histology and the histological study of gray matter in general will yield perhaps our earliest comparative insight into synapse-changes in man. From this point of view the study of cellular and fibrillar gliosis in gray centers assumes a new importance, since the penetration of neuroglia cell processes and of neuroglia cell fibrils between surfaces of separation, or the overgrowth of these structures to form fresh surfaces of separation, must modify reflex arc functions in a degree. Not alone the malnutrition of gray centers and the consequent atrophy of cells with their adnexa, but also the secondary and reactive effects of the ensuing interstitial reparative process of gliosis will affect the synapses, suspending the functions of some and altering the functions of others.

Functional Changes in Reflex Arcs.

At the risk of obscuring rather than clearing up the issues, we may here briefly mention the functions of reflex arcs which might theoretically be altered in disease together with some examples of such alteration.

Let the reflex arc consist of three structures: 1, an effective organ (muscle or gland) in which effects are to be obtained; 2, a conducting organ (nerve fiber or path) running to the muscle or gland; and 3, a receptive organ (sensory cell or other afferent cell). These structures have been briefly termed *effector*, *conductor*, and *receptor*. The afferent portion of the reflex arc is that portion of the arc up to the effector organ and the nerve cell which stands in immediate relation to the effector organ. Thus, the knee-jerk is brought about by a reflex arc which depends upon the integrity of sensory leg fibers, upper lumbar spinal cord, and motor fibers to the quadriceps. All that portion of the knee-jerk apparatus from sensory cells up to but not including motor cells of the upper lumbar anterior horns is defined as the afferent arc. The afferent arc is brought into relation with the motor part of the whole reflex arc in the gray matter of the anterior horns; here is placed the synapse of the reflex apparatus upon which the knee-jerk depends.

The reflex arc will fail to work in case any of its elements is destroyed or for the moment paralyzed. The synapse is the most delicate element in the apparatus and alters its functions in response to slighter stimuli than do the motor and sensory fibers. As between the motor and sensory fibers, the functions of the former are more quickly and readily suspended than are those of the latter.

1. The reaction-time of the reflex arc may be lengthened or shortened by disease (alterations of *latent period* between time of stimulus and time of discharge).

2. The duration of the discharge by a reflex arc may be lengthened or shortened by disease (alterations of *after-discharge* of the arc, to be distinguished from alterations in the muscular or glandular effect which may be due to local or general non-nervous causes).

3. The habitual correspondence or rhythm between stimulus and discharge may be altered, so that clonic contractions may be substituted for tonic, and *vice versa*.

4. The usual direct ratio between energy of stimulus and energy of discharge may be altered so that weak stimuli may evoke unduly energetic discharges.

5. The conditions underlying *summation of stimuli* may become altered, so that a succession of abnormally weak stimuli, or a briefer series of stimuli than usual, or a series of stimuli at longer intervals than usual, may evoke discharges.

6. Abnormal *fatigability* may occur in disease. This property, as well as 5, is characteristic of the gray matter (the synapses) rather than of nerve trunks.

7. The duration of the *refractory phase* (inexcitable period of a mechanism, first demonstrated in the heart but found also in spinal and other reflexes) may be altered.

As in the normal mechanism, so in the diseased nervous system the reflex arc mechanisms are characterized by much wider variations taken as a whole than are the nerve trunks examined by themselves. The reflex arcs are decidedly more susceptible to deficient oxygenation and to anesthetics than are the nerve trunks. All data unite in pointing to the gray centers as most important sites of disease. It is suggestive to consider that the interneuronic connections characteristic of gray matter (the synapses or physical surfaces of separation of the neurones) are the foci of greatest importance in essentially nervous diseases.

It has been pointed out that the *neurone unit* with which the histology of the nervous system culminates is not an effective unit of great importance for muscular or glandular action. The *reflex arc* forms the true functional unit of the nervous system; and one element of the reflex arc, the *synapse*, is its most conspicuous element, inasmuch as the most important variations of reaction time and of stimulability in general belong to the synapses. In the higher organisms, however, it is evident that single reflex arcs, however indispensable to the organism, are subordinate in importance to the higher function of coördinating the activities of the various reflex arcs.

GENERAL AND FOCAL SIGNS AND SYMPTOMS.

The simple reflex arc is an abstraction. We deal in the organism with coördinated reflexes. The coördination of reflexes serves (1) to bring a single result out of reflex arcs which are simultaneously active and (2) to accomplish a single purpose out of reflex arcs which are working in series. It is evident that disease can very readily perturb wide fields of activity with relatively minute lesions.

Disorders of function in the nervous system are said to be exhibited in two special kinds of symptoms and signs, *focal* and *general*. In truth the so-called general symptoms are themselves also focal. They are properly termed general, because we can deduce from them the fact of a general involvement of the whole (intracranial) apparatus. The general symptoms are actually focal, because, however general the involvement, certain parts of the apparatus succumb before others. Such symptoms are diagnostic in that they form a characteristic series.

As *general symptoms* of brain disease may be counted *headache*, *vomiting*, *vertigo*, *disorder of consciousness*, changes of *pulse* and of *respiration*, *increase of temperature*. *Choked discs* are perhaps the most important sign of heightened intracranial pressure.

The occurrence of *headache alone* has no significance as a *general* symptom in the above sense. Headache and *vomiting* together are more suggestive of brain disease. But this association of symptoms is also found in infectious diseases, in uremia, in migraine, and in gastric disorders. However, although there is nothing characteristic in the headache of brain disease, "cerebral" vomiting is a characteristic form of vomiting, being easy or even projectile, without nausea, and independent of eating.

Vertigo, like headache, taken by itself scarcely points to brain disease, and only in association with other symptoms is vertigo of diagnostic value. Vertigo should perhaps be classed with disorders of consciousness, along with *drowsiness*, *heavy sleep* and *coma*.

The *grades of unconsciousness* are classified somewhat loosely according to strength of stimulus required to awaken. In *drowsiness* the patient is readily awakened, only to fall asleep forthwith. In heavy sleep (*sopor*) the patient can be awakened only by strong stimuli, but the peripheral reflex arcs are still active, so that, *e.g.*, the knee-jerk can still be brought out. In *coma* the patient is unconscious, but also cannot be aroused by strong stimuli. In the deepest forms of coma the peripheral reflex arcs are no longer active.

The changes of pulse, respiration, and temperature vary in brain disease and depend largely upon indirect effects wrought upon the medulla. Thus a *slow pulse* is characteristic in the beginning, though it may alter to a rapid rate later. It is remarkable that, in the presence of general brain disease, fever frequently fails to be attended with a rapid pulse.

The *respiration* is frequently of the *Cheyne-Stokes* type. After several light breaths, there follows gradually increasing noisy respiration with snores (stertor). Then the more superficial breathing gradually supervenes, followed by absolute apnoea. This cycle of changes is then repeated. In the phase of apnoea the pupils are usually narrow and the pulse slow.

Concerning *temperature*, most remarkable is the frequent lack of elevation thereof in general infectious diseases of the brain and in cases of brain abscess with generalized pressure.

Disorders of blood-supply affect first of all the medulla oblongata and especially *the breathing center*. Later the cerebral cortex is affected, and *consciousness becomes clouded*. It is remarkable that the same degree of circulatory disorder when become chronic, as in cases of pronounced venous stasis or arterial anemia, fails to produce bulbar or cortical symptoms. This fact seems to argue an habituation of these centers to abnormal conditions.

Fainting spells are general symptoms in the sense that they involve a great part of the central apparatus. The cerebral cortex in a faint seems to be affected as in light narcosis. The breathing center is not affected. The pulse is slow and interrupted. On account of the occurrence of fainting spells in anemic and arteriosclerotic subjects, it might be thought that the spells are the result of circulatory disorder. The spells occur also, however, in healthy persons as "psychical effects," and, if a fainting spell were truly a circulatory disorder, the breathing center ought to be affected.

The *anemic series* of phenomena, headache, tinnitus aurium, eye-sensations, vertigo, and feeling of lassitude, may be mentioned under the head of general symptoms. These phenomena are perhaps better regarded as due to changes of metabolism than to changes going on in central nervous tissues.

The most important series of general signs and symptoms referable to the nervous system is the series due to *heightened intracranial pressure.* These phenomena are separable into the results of indirect (latent) pressure and those of direct pressure.

The effects of *latent increase of pressure* are headache, general mental and bodily weakness, and choked discs.

The effects of *direct increase of pressure* (due to a degree of pressure sufficient to compress the arteries) are stupor, vomiting, slowing of pulse and respiration, and general epileptiform convulsions.

The effects of violence upon the encephalon belong in the present group of signs and symptoms. In concussion (*commotio cerebri*) the subject is pale, unconscious, and lax, with weak respiration and a soft small pulse sometimes slow, sometimes rapid. Vomiting occurs.

In rapid attacks of *cerebral hemorrhage* consciousness is lost with slowing of pulse and respiration. The temperature, at first low, later rises. Similar symptoms attend *cerebral embolism.*

The *focal signs and symptoms* of nervous disease may be divided into *motor* and *sensory.* The motor signs and symptoms fill much greater space in the books than the sensory signs and symptoms, for several reasons. First, the paralyses and irritative disorders of movement are more readily accessible to observation. Secondly, the effect of disorders of sensation is very frequently to bring about disorders of motion, as when pain produces muscular immobility, or as when the loss of centripetal impulses from joints and muscles produces ataxia. Thirdly, with injuries to an apparatus containing both motor and sensory fibers, the sensory fibers are more resistant than the motor fibers, and accordingly paralysis of motion sets in before paralysis of sensation *ceteris paribus*.

MOTOR DATA.

The *motor signs and symptoms* are :

1. *Paralyses*, (strictly) losses of power to execute certain voluntary movements. (The term *paralysis* is more or less figuratively used of sensation as well as of motion and is occasionally used of psychical processes, *e.g.*, paralysis of ideation. More legitimate is the use of the term for loss of involuntary movements, *e.g.*, paralysis of intestine. Used alone, however, the term as a rule refers to a loss of power to execute voluntary movements.)

2. *Pareses*, diminutions of power to execute certain voluntary movements (partial paralyses).

In the case of paralyses and pareses, the diagnostician alleges a nervous origin only after excluding several other possible origins for the loss of motion. Loss of motion may be due to diseases of *joints*, *bones*, and *muscles* as well as to diseases of the nervous system.

3. *Ataxias*, uncertain or awkward combined movements.

4. *Tremors*, oscillatory muscular movements about a single axis. The rate, extent, and number of involved muscle groups vary. Sometimes tremors occur when the subject moves the part (*intention-tremors*) ; sometimes they occur only when the parts are quiet. Tremors cease in sleep.

5. *Choreiform movements*, spasmodic, non-rhythmical involuntary movements, often of wide excursion.

6. *Tics*, intermittent but habitual convulsive movements, as a rule reproducing some reflex or automatic natural movement. Tics either cannot be checked by action of the will or are checked only at the expense of an unpleasant feeling. Some tics are preceded by pain (*tic douloureux*).

7. *Habit-spasms* (functional spasms), transient contractions in muscle-groups upon the attempt to perform some habitual combined movement. The best-known example of habit-spasm is *writer's cramp*. The affected muscles function perfectly well

for other purposes than those of the habitual movements in question.

8. *Convulsions,* sudden involuntary muscular contractions. Convulsions occur in two forms, clonic and tonic. *Clonic convulsions* occur as a more or less irregular *series of contractions* of a given muscle or group of muscles, *with intervals of relaxation.* The movements in a given series of clonic convulsions are apt to be unequal in duration and in energy. *Tonic convulsions* occur as relatively lasting contractions with rigidity of the involved muscle groups. The strength of the contractions varies. In the midst of the continuous contraction occur slight heightenings and lowerings of the muscular tension. The contraction, when heightened and maintained at the maximum for a considerable time, is termed a state of *tetanus.* Tonic contractions differ essentially from clonic contractions in that *tonic contractions show no intervals of complete relaxation.*

Convulsions may be divided into *partial* and *generalized* convulsions. Either partial or generalized convulsions, *when repeated,* constitute epilepsy. *Partial or Jacksonian epilepsy* exhibits repeated convulsions involving a muscle-group or muscle-groups, a limb, or half of the body. Repeated generalized convulsions constitute *epilepsy proper.* It is customary to separate the cases of repeated generalized convulsions without obvious cause (*idiopathic* or *essential epilepsy*) from those with a well-defined anatomical basis (*organic epilepsy),* from those occurring as incidents of other diseases (*secondary epilepsy*), and from those due to peripheral irritation (*reflex epilepsy*).

9. *Contractures,* permanent contractions with fixation of parts, are of two kinds, *active* (spastic) and *passive* (paralytic). A limb in active contracture elastically resists change of position. The rigidity is subject to very slight variations. Under narcosis, in sleep, and after application of a tourniquet, the contracture ceases. A limb in passive contracture is in complete fixation which cannot be reduced mechanically or under narcosis. Passive contractures occur in paralyzed limbs; but the contractures are not due directly to the paralyzed muscles, but rather to the preserved antagonistic muscles. Passive contractures occur also in joint and muscle diseases. Of active contractures, it may be said that they depend directly upon an alteration in the central nervous system. On the contrary, passive contractures depend more on non-central conditions.

Kernig's sign, found in various kinds of cerebrospinal meningitis, is the name given to a latent contracture such that, with the subject lying on his back, his legs are flexed on the hip and knee and cannot be straightened out.

Trismus is a contracture involving muscles of the jaw. *Risus sardonicus* depends upon contracture of face muscles.

Opisthotonos, an arching backward of the body, and *emprosthotonos*, an arching forward of it, are contractures occurring as part of a state of *tetanus* incidental to several infectious diseases.

10. *Catalepsy* implies an incapacity to move by action of the will certain muscles and a tendency to retain postures imparted to the body from without. The limbs are not in contracture, but are supple and may be moved like those of a doll (*flexibilitas cerea*).

11. *Athetosis* is constituted by involuntary, slow, nonrhythmical, irregular movements of slight excursion and without cessation. These movements usually cease with sleep and can be curbed a little by the will. They are exaggerated by emotion and may then become extensive enough to warrant the term choreiform.

12. *Hypotonia*, diminution of tone. Whereas the average subject lying in a horizontal position cannot endure without pain the raising of a leg beyond the vertical plane, the subject of tabes, for example, will sometimes readily permit, through hypotonia, the assumption without pain of difficult postures usually open only to an acrobat: the leg can be flexed beyond the vertical plane even to an angle of 120°–130°.

SENSORY DATA.

The *sensory signs and symptoms* are due in part to alterations in the two kinds of sensory apparatus, the apparatus of special sense and that of the organic sense, but in part to alterations in the conducting and central apparatus. These phenomena may be divided into the *objective*, *i.e.*, such as may be elicited on examination, and the *subjective*, *i.e.*, such as the patient himself reports.

Sensory signs and symptoms comprise :

1. *Anesthesia*, abolished sensation.
2. *Hypesthesia*, diminished sensation.
3. *Hyperesthesia*, exaggerated sensation.
4. *Paresthesia*, perverted sensation.

The loss of pain sense is specially designated *analgesia*, diminished pain sense *hypalgesia*, exaggerated pain sense *hyperalgesia*. Special designations for alterations in various qualities of sensation are built on the same principle, as *thermoanesthesia*, *hypothermesthesia*, *hyperthermesthesia*, etc. Terms constructed upon the same plan are in common use for alterations in the sphere of smell (*anosmia*, *hyposmia*, *hyperosmia*, *parosmia*) and in the sphere of taste (*ageusia*, *hypogeusia*, *hypergeusia*, *parageusia*).

Sensations may be otherwise normal, but their impulses require more time than usual to reach higher centers. Such an augmentation of the *threshold value* for consciousness is characteristic, for example, of pain sensations from the skin in tabes dorsalis.

Just as in the motor field certain non-nervous origins for paralysis had to be considered, so there are non-nervous origins for certain changes of sensation. *Itching* is a sensation or combination of sensations perhaps due to abnormal excitation of the pressure spots in the skin. But itching is characteristic, not of nervous disease, but rather of certain skin-diseases, jaundice, diabetes, pruritus. *Paresthesia*, on the other hand, as exemplified in tinglings, or ant-crawling feelings (formication), is a condition which fails to be found in skin diseases and in the other diseases mentioned, but is characteristic of diseases of peripheral or spinal nerve paths. One theory of paresthesia is that it is due to an irritation of the conducting fibers for pressure impulses.

Disorders of Reflex Movement.

The total activity of the nervous system may be construed as the activity of combined reflex arcs. A few of these arcs, whose activity is specially accessible to observation, produce the *reflexes* in the narrow sense of certain *involuntary movements invariably produced by certain stimuli under normal conditions*. These accessible reflexes, which are of major diagnostic importance, are divided for convenience into the *superficial reflexes* and the *deep reflexes*. A typical example of a superficial reflex is the *closure of the eyelids* upon stimulation of the conjunctiva. The most significant deep reflex from the diagnostic point of view is the *knee-jerk*, produced by contraction of the quadriceps femoris after a blow upon the ligamentum patellæ.

The presence of a reflex signifies the intactness of its arc. The *absence of a reflex does not* necessarily *signify a lesion of its arc. The heightening of a reflex* has two possible meanings: *means either irritative conditions* at some point in the arc *or the suspension of normal inhibitory impulses* from elsewhere. *The lowering of a reflex* likewise has two possible meanings: *means either alterations* at some point *in the arc* or in certain cases a *heightening of inhibitory impulses* from elsewhere.

The *intensity* of the reflexes varies in different individuals. Certain *reflexes* (even the knee-jerk) are *absent in individuals otherwise normal.* So-called "*nervous*" persons show a greater intensity of various reflexes, due both to a superior excitability of the reflex arcs in question and to the smaller play of inhibitory impulses from outside the arcs in question. *Fatigue, marasmus, and cachexia increase the reflexes,* perhaps operating in the same two ways. The febrile *infectious diseases* operate sometimes to increase, sometimes to lessen, sometimes to leave unaltered the reflexes. The *death agony shows a decrease of the reflexes,* and a decrease of reflexes is sometimes a signal of fatal issue.

The disappearance of *tendon reflexes,* early *in tabes dorsalis,* is attributed to a lesion in the reflex arcs involved. Thus the knee-jerk, which is effected through an arc whose synapse lies in the gray matter of the third lumbar segment, is lost or decreased early in many cases of tabes dorsalis. This loss or decrease is ascribed to a degeneration of the intradural portion of the ganglio-spinal neurones at that level. By this means the impulses starting in the ligamentum patellæ and running along the leg nerves (which are intact so far as our present technique permits us to say) fail to come into relation with the cells of the anterior cornua of the cord. The course of these cases occasionally demonstrates a point of theoretical importance. Occasionally in the course of tabes dorsalis there supervenes a hemiplegia, due to an interruption of one pyramidal tract above the tabetic lesion (*e.g.*, hemorrhage into the internal capsule). Under these circumstances the *knee-jerk may return* on the paralyzed side. The return of the knee-jerk under these circumstances is best explained by assuming (1) that the original loss of knee-jerk in the course of tabes was not due to a totally destructive lesion in the knee-jerk reflex arc, but was due rather to a partially destructive lesion such that the normal down stream of inhibitory impulses was able to suppress the knee-jerk altogether, and (2) that the return of the knee-jerk is rendered possible by cutting off the normal down stream of inhibitory impulses and the release of the knee-jerk reflex arc function.

The conception of the *inhibitory function* of impulses passing from higher centers to various reflex arcs is of high diagnostic importance. The conception needs supplementing in one respect. It is obvious that a transverse destructive or otherwise paralyzant lesion of the spinal cord higher than the third lumbar segment should be followed by an increase of the knee-jerk owing to the loss of inhibitory impulses from above. *If the transverse lesion is absolutely complete* (*e.g.*, in total severance of the cord tissues by stab-wound or extensive fracture), *the knee-jerks are and remain absent.* The explanation of this is obscure. The point offers few diagnostic difficulties since transverse lesions so complete as to involve destruction of all nervous communications between two segments of the spinal cord are rare.

The superficial reflexes are extensive responses to slight stimuli. They are slower than the tendon reflexes and much more dependent on the will. The synapses of the reflex arcs of the superficial reflexes are found in several parts of the nervous system. A number of their synapses are found in the cerebrum. The superficial reflexes are often absent when the tendon reflexes are increased.

Light upon the spread of reflexes has been thrown by *experimental tetanus*. Although in tetanus naturally occurring in man the onset is with trismus, in experimental tetanus the rigidity first occurs in muscle groups near the site of inoculation. The toxine reaches the nervous system, not by way of the blood and lymph paths, but by way of the axis cylinders. By direct inoculation into the spinal cord, the incubation period of the rigidity can be shortened by more than two hours. The toxine acts directly upon the motor cells and tonic contractions follow. *Reflex contractions* ensue only upon the extension of the toxine to the sensory part of the arc involved.

The reflexes are of diagnostic value on account of (1) the evidence afforded concerning the local state of the nerve tissue containing the reflex arcs (here the synapses are of predominant importance), and (2) the localizing evidence afforded by the presence or absence of certain reflexes in combination. Take as example a transverse lesion of the thoracic spinal cord. The lower part of the body will present paralysis of voluntary motion and loss of sensation (interruption of communication with the cerebrum, cerebellum, and possibly other higher centers). Moreover, the bladder and rectum are no longer under voluntary control. The knee-jerks are lively, there is dorsal instead of plantar flexion of the toes on stroking the sole of the foot (Babinski's sign), clonic contractions occur in the foot upon sharp flexion of the foot when the leg is extended at the knee (ankle clonus). The exact localization of the transverse cord lesion requires more data than these. Suppose the abdominal reflexes are preserved : the lesion can be placed higher than the ninth thoracic nerve.

We test the skin reflex by simple touch, by tickling, by pricking, by stroking with a pencil, by touch with a cold object and the like. There are three skin reflexes which are of great importance. The *abdominal reflex* is a reflex in the epigastrium, the umbilical region, and in the lateral portions of the abdomen. The synapse of the reflex arc corresponding to the abdominal reflex exists in the lower thoracic cord. This reflex is, as a rule, present in normal persons, especially in young persons with tense abdomens. The *cremasteric reflex* has the synapse of its arch in the lumbar cord. The *plantar reflex*, which has come into such prominence of late under the name of Babinski reflex, is a reflex on touching, stroking or pricking the sole. Dorsal flexion of the toes is understood, nowadays, to mean disease of the pyramidal tracts or of the motor apparatus at some point above the anterior horns.

The most important of the tendon reflexes is the knee-jerk. If the subject clinches his fists, then we speak of *reënforcement* of the knee-jerk. And by this means the knee-jerk may be brought out in subjects that would otherwise fail to show it.

Other important tendon reflexes are :

The *Achilles reflex*, to produce which the foot is held passively in dorsal flexion and the Achilles tendon maintained in light tension whereupon a stroke upon the tendon produces a reaction.

The *triceps tendon reflex* is produced by a blow upon the triceps tendon in a condition of flexion of the forearm.

The *periosteal reflex* of the radius and ulna is produced by stroke upon the ends of these bones in a condition of moderate flexion of the arm.

The *masseter reflex* is produced by stroke upon the lower teeth with the mouth moderately wide open.

VASCULAR AND GLANDULAR DISORDER.

Nervous disorders affect the activity of the *vessels* and the *glands*. Vasomotor disorders are exhibited in cold or over-warm parts, in pallor or redness, dependent upon vascular contraction or paralysis. We may get paralytic dilatation or paralytic contraction. The glands may exhibit increase or diminution or loss of function. Examples are salivation, dryness of the mouth, hyperidrosis. Nervous edema affects certain parts locally and may occur with or without demonstrable vasomotor disorder. Besides the vasomotor disorders an important group of symptoms in nervous diseases is furnished by *atrophic disorders*. Whatever be our opinion as to the existence of separate trophic nerves, it is at any rate beyond cavil that certain parts in nervous diseases may suffer a loss of resistance to injury. Besides the muscular degeneration which follows injury to motor nerves, we may include under this head changes in the growth of bone and in the composition of bone occurrring in connection both with paralysis and with anesthesia; also changes in the skin (thickening, thinning, or formation of glossy skin) and thickening, deformities and falling out of nails. As a result of these changes combined with effects of anesthesia, we frequently observe in anesthetic parts, decubitus, inflammations, gangrene, diseases of the joints, undue tendency to fracture.

SKETCH OF LOCALIZATION IN NERVOUS DISEASES.

If we subject a mixed nerve to pressure, certain irritative phenomena ensue, namely, paresthesias, pain, convulsive movements. If we increase the pressure, we procure a paralysis which may persist after the pressure is removed. In case, however, the structure of the fiber is not seriously damaged, then the electrical irritability of the muscles remains unaltered and no muscular atrophy results. Motion returns after some hours, days or weeks, and we speak of the condition as *slight peripheral paralysis*. If the pressure is still more severe, then the paralysis will be accompanied by reduction or loss of sensation. The muscular fibers atrophy, and there is a partial reaction of degeneration electrically. This condition gets well only after longer periods, from several weeks to one or three months. We should term such a paralysis a *moderately severe paralysis*. If we subject the nerve to such strong pressure that the fibers are destroyed, then the paralysis and anesthesia are complete and the severe paralysis lasts till the degenerated nerves are regenerated. This regeneration will scarcely occur under four months, and may take far longer in case there is considerable scar tissue to impede the regeneration. With the same degree of injury the motor fibers suffer more relatively than do the sensory fibers, so that the degree of reduction in sensation does not run parallel with the degree of reduction in motion.

The distribution of muscular paralyses and atrophies varies with the site of the lesion which produces them. This distribution follows one of four types :

I. Peripheral.
II. Radicular.
III. Medullary and spinal.
IV. Cerebral.

Paralyses and atrophies of *peripheral* origin are grouped according to the anatomical distribution of the nerves or plexuses involved by lesion. Trauma or pressure may produce effects strictly limited to certain muscle groups. Infectious or toxic injuries to the peripheral nerves produce effects, as a rule, more marked distally (as in the hand or foot).

The *radicular* paralyses and atrophies ensue upon lesion of the anterior roots and of the trunks of origin in the great plexuses. Almost all the muscles are innervated by fibers in at least two anterior roots. The trunks of origin of the cervical, brachial, lumbar, and sacral plexuses already contain an admixture of sensory with the motor fibers : the paralyses and atrophies of radicular origin are therefore attended by sensory disorders of similar strict localization.

With respect to the *myelopathic* paralyses and atrophies, which ensue upon lesion of the pyramidal tracts and of the anterior horns respectively, the weight of evidence at present indicates that they follow in general the radicular distribution. Other types of distribution are logically possible and have at various times been assumed, such as a limited distribution with a given nucleus for a given muscle group, or a segmentary (metameric) distribution, or a more diffuse distribution of non-radicular type. The radicular type of distribution is demonstrated well at times in cases of syringomyelia, hematomyelia, and acute anterior poliomyelitis, but may be less distinctly seen in diseases of a more diffuse extent, as in amyotrophic lateral sclerosis, wherein the paralysis and atrophy follow a double lesion of pyramidal tracts and anterior horns.

The distribution of paralyses of *cortical* origin is rarely as sharply limited as the distribution of muscular contractions excited electrically at the cortex. The lesions are almost without exception too extensive for such focal results; and results less gross than a hemiplegia or a monoplegia are rare in cortical lesions, and still rarer in subcortical or capsular lesions. The muscle groups which subserve the more specialized functions are more apt to be incurably involved in these lesions than the muscles of lower function.

Functional Effects of Lesion in Peripheral Nerves.

Olfactory nerve. *Hyperosmia, parosmia, anosmia.* In testing for alterations in smell care must be taken not to use substances which also irritate the trigeminus (*e.g.*, ammonia).

Optic nerve. *Alterations in sharpness of vision, light sense, color sense.* The *visual fields* may exhibit alterations, chiefly in the line of defect. Total destruction of the optic nerve produces *amaurosis with dilated pupil.* Partial injury of fibers leads to weak vision *(amblyopia).* Injury to optic tracts leads to *hemianopsia.* In case the right optic tract is affected, blindness ensues in both right halves of the retina. In case the chiasma is subject to lesion we get *temporal hemianopsia* in both eyes.

Oculomotor nerve. With paralysis of the oculomotor nerve, the levator palpebræ is involved, yielding *ptosis.* The involvement of the internal, superior, and inferior recti and of the inferior oblique muscles produces *divergence* of the eyeball *outward and downward,* and *crossed diplopia.* Only motion outward and slight rotary motion remain possible. Involvement of the sphincter iridis produces dilatation and stiffness of pupil. Involvement of the ciliary muscle destroys the power of accommodation.

Trochlear nerve. Paralysis of the superior oblique muscle produces inability to turn the eye downward, and slight divergence inward with diplopia in the lower half of the visual fields.

Trigeminal nerve. *First branch.* Anesthesia of the skin from the middle of the scalp down to and including the upper eyelid and the bridge of the nose, externally to the temporal line, internally to the middle line, besides an anesthesia of the conjunctiva, the cornea, the iris, and the other membranes of the eye, a portion of the dura mater, a portion of the nasal mucosa, with disturbance in tear secretion. Necrosis of the cornea (ophthalmia neuroparalytica) may follow.

Second branch. Anesthesia of the skin of the lower lid, of the cheek, of the upper lip, of the mucous membrane of the upper jaw, a portion of the nasal mucosa, of the uvula, a portion of the dura mater, of the mucosa of the middle ear, anesthesia of the upper teeth and disorder of taste.

Third branch. Anesthesia of the lower lip and chin, of the lower part of the cheek, of the region of the ear and temple, a portion of the dura mater, the tongue, the mucosa of the lower jaw and cheek, the lower teeth, paralysis of the muscles of mastication and of the tensor tympani, and disorder of salivation.

ABDUCENS NERVE. Paralysis of the external rectus muscle with external strabismus and diplopia upon looking toward the side of the paralysis.

FACIAL NERVE. Paralysis of the muscles of expression. The forehead cannot be wrinkled, the eyes cannot be closed, the lips cannot be moved.

ACOUSTIC NERVE. *Cochlear branch.* Subjective noises, and deafness. *Vestibular branch.* Dizziness, and disorder of equilibrium. If tinnitus aurium and vertigo coexist and occur in attacks, we have what is known as Menière's symptom.

GLOSSOPHARYNGEAL NERVE. Loss of taste (ageusia) in the back of the tongue.

VAGUS NERVE. Anesthesia of a portion of the skin of the ear, of the larynx, probably also of the esophagus, of the trachea, and the bronchi, possibly of the stomach. Paralysis of the esophagus, probably disturbance of motion of the stomach, and disorder of circulation and respiration.

HYPOGLOSSAL NERVE. Paralysis of the tongue. The tongue when protruded forms a concavity toward the side of the lesion. The diseased half becomes atrophic. Motion suffers very little with one-sided disease, but disappears with bilateral disease.

SPINAL NERVES. The upper four *cervical nerves* when injured yield anesthesia of the back of the head, the anterior and lateral parts of the neck, the upper shoulder region as far down as the scapula, and paralysis of most of the neck muscles and of the diaphragm. The lower four cervical nerves supply the skin of the back of the neck and certain deep neck muscles by means of their posterior branches. Their anterior branches form the brachial plexus.

The *thoracic nerves* yield upon lesion of their posterior branches anesthesia of the back and paralysis of the spinal muscles, and upon lesions of their anterior branches (that is to say the intercostal nerves), anesthesia of the skin of the chest and abdomen with immobility of the upper half of the chest, disturbance of expiration, and paralysis of the abdominal muscles. Disturbance also of defecation and micturition. Prominence of the abdomen and lordosis of the lumbar vertebral column, inability to rise from a horizontal position without support from the arms.

The *upper four lumbar nerves.* Posterior branches: Anesthesia of the upper nates and paralysis of the erector muscles of the trunk, of the quadratus lumborum, and of the deep muscles of the lumbar spine. Disorders following lesion of the anterior branches lie in the region supplied by the lumbar plexus.

Fifth lumbar and the sacral nerves. Lesion of the posterior branches produces anesthesia over the sacrum. Lesion of the anterior branches produces disorder in the region controlled by the lumbar plexus.

SYMPATHETIC NERVES.

Lesion of the *cervical portion* produces narrowing of pupil with loss of capacity to dilate reflexly, but with motion otherwise well preserved. Narrowing of palpebral fissure, recession of the bulb, dilatation or sometimes contraction of the vessels, anidrosis or sometimes hyperidrosis on the diseased side of the head and slight flattening of the diseased side of the face. Lesion of the *thoracic and abdominal* part of the sympathetic system may produce slowing of the heart activity (cardiac nerves) and disturbance of the activity of the intestine, abdominal viscera, and organs of the pelvis (splanchnic).

LOCALIZATION IN THE SPINAL CORD.

It is difficult to distinguish disease of the lower end of the spinal cord and disease of the *cauda equina* in respect to the symptoms which they produce, nor does this question arise practically, because both parts are as a rule involved in the one disease. If we destroy the *sacral cord,* we produce atrophic paralysis and anesthesia in the region supplied by the sciatic nerve, anesthesia of the sexual parts, and of the rectal region, and complete paralysis of the bladder and intestine. If only the *lower* end of the sacral cord is affected, then there is no longer paralysis of the legs, and we get merely paralysis of the bladder and intestine, anesthesia of the sexual parts, and of a triangle of skin at the posterior portion of the thigh. If we put the lesion higher, namely in the *lumbar cord,* we produce paralysis of the legs and anesthesia up to the brim of the pelvis, paralysis of the bladder and intestine (in the sense that their activities are withdrawn from voluntary control) and atrophic paralysis of those muscles whose anterior horn cells are destroyed. In case the *upper* lumbar cord is destroyed we get atrophy of the quadriceps with loss of knee jerk, of the abductors and of other muscles supplied by the lumbar plexus. In case the *lower* lumbar cord is affected we get atrophy of the glutei and in the perineal region; and in this case the quadriceps is free and the anesthesia reaches only to the upper third of the thigh.

The simplest picture is produced by lesions of the *thoracic cord.* There follow paraplegia and anesthesia of the lower part of the body, and the bladder and intestine are withdrawn from control by the will. The upper limits of the anesthesia reach to various heights, as to the umbilicus, to the border of the ribs, to the fifth or third rib. The knee jerk is as a rule very lively, the ankle clonus appears, and after a time the legs get somewhat stiff. The Babinski reflex is often shown. The abdominal reflex may be preserved in case the lesion lies above the ninth thoracic nerve; otherwise a portion of its reflex arc is destroyed.

Lesions of the *cervical cord* show paralysis of the legs and of the back, but also paralysis and anesthesia of the arm. In case the lesion has a certain extent, then a portion of the anterior horn cells may be destroyed and a portion of the arm muscles will degenerate. *Eighth cervical:* paralysis and atrophy of the small muscles of the hand and of the flexors of the wrist. *Seventh cervical:* paralysis and atrophy of extensors of the wrist. *Sixth cervical:* paralysis and atrophy of serratus magnus, triceps, latissimus, teres major, pronators, subscapularis. *Fifth cervical:* paralysis and atrophy of deltoid, supinators, biceps, and brachialis internus. *Upper cervical:* lesion fatal on account of involvement of the phrenic nerve.

SYMPTOMS OF DISEASE OF THE PONS AND MEDULIA.

The pons and medulla contain in a small space the most important paths for muscular movement, for sensation, for the muscular side of speech, for swallowing, circulation, respiration, etc. A focus in the medulla may be small and still produce manifold symptoms. The *dorsal region* (1) of the pons and medulla contains several nuclei of the cranial nerves and their root fibers. Ventral to the nuclei of the cranial nerves in the *middle region* (2) lie sensory paths from the contralateral sides of the body, and in the *ventral region* (3) beneath the crossed sensory paths lie the motor paths from the cerebrum likewise for the opposite halves of the body. *Laterally* to these (4) lie the cerebellar paths.

Foci of disease in the upper or dorsal part of the pons and medulla will produce cranial nerve symptoms alone. In case the foci are larger and stretch ventrally, then over and above the cranial nerve symptoms we shall discover disorder of sensation in the opposite side of the body, and in case the lesions reach so far ventral as to touch the pyramidal tract, then we shall get besides the crossed sensory disorder, also disorder of motion.

Since an interruption of the long (sensory or motor) paths will produce the same symptoms whether that interruption takes place in the cerebrum or midbrain or wherever, it is clear that from a disorder of sensation or motion we can never conclude a disease in the pons or medulla. For the *diagnosis of a disease of the pons and medulla* we require a *combination of symptoms in the sensory or motor part with* symptoms relating to one or other of the *cranial nerves.* It may be remarked that disorder of the nuclei of the cranial nerves will produce atrophy of the corresponding muscles upon precisely the same principle according to which disease of the anterior horn cells produces atrophy of their appertaining muscles. Disease of the pons and medulla shows an affection of the cephalic or cranial region upon the side of the lesion, combined with an affection of the trunk and of the extremity upon the side opposite the lesion. This condition we know as alternating or *crossed paralysis.* This simple relation of things needs to be limited in one direction. Of course the cortical paths which lead to the nuclei of the cranial nerves must also run through the medulla. They may also be affected by lesions.

For example, we may have a *left-sided lesion* in a certain part of the pons which shall produce also a *paralysis of the right facial.* This paralysis of the right facial in the case of a left pontine focus is due to the fact that the fibers to the right facial are derived from the left hemisphere and are caught in the lesion before decussation.

Old inflammatory lesions at the base of the brain often involve asymmetrically the superficial origins of various cranial nerves, and hence mimic the effects of central pontine or medullary lesions. The organization and contraction of the exudates at the base of the brain and the contraction of the reactive gliosis underlying the meninges may even produce pressure enough upon the long tracts so as very effectually to mimic lesions of the central portion of the pons and medulla.

In the case of diseases affecting the medulla we shall naturally be concerned with the hypoglossal, facial, and vagus. The best clinical illustration of disease of this region is the disease known as progressive bulbar palsy. The symmetry of the effects of this lesion, and the strict limitation of the symptoms to motion and the slow progressive course of the disease facilitate the diagnosis. Of course it is easy to see that effects in the hypoglossal, facial, and vagus areas of supply can readily be produced by lesions of the cerebrum; but although we can produce paralysis in special areas by means of lesions of the cerebrum, it will naturally be impossible to produce atrophy of the muscles in question with the reaction of degeneration. Progressive bulbar palsy is the characteristic systemic disease of the medulla. Over against this systemic disease of the medulla may be set the protean manifestations of arteriosclerosis. The isolated and non-systemic effects in these cases are due to the situation of cysts of softening. Other characteristic lesions of the medulla may be found in tabes, and here it may not be possible to distinguish nuclear from tract degeneration. In the case of diseases at the base of the posterior fossa of the skull we rarely fail to get the results of irritation of the dural nerves in *headache* and a disease of several nerves of the medulla *without* special systemic arrangement.

The pons contains the pyramidal tracts ventrally, the sensory paths in the fillet, and the nuclei of the trigeminus. Naturally we cannot make the differential diagnosis of disease of the lower part of the pons against disease of the upper part of the medulla. It is said that primary disease affecting the nuclei of the trigeminal nerves is only found in tabes. Paralysis of the muscles of mastication with or without anesthesia follows. Larger areas in pons produce alternating (crossed) paralysis. Unilateral lesions affecting the fillet produce hemianesthesia on the other side of the body. When we rise to the peduncles we find hemiplegia due to lesions of the pyramidal tract and hemianesthesia due to lesions of the tegmentum. On account of the small space through which the pyramidal tracts and the fillet fibers run at this point, it is relatively frequent to find disorders of sensation together with hemiplegia. Neither the hemiplegia nor the hemianesthesia will serve to place the lesion in the peduncle. A localizing diagnosis of disease of the peduncle is only possible when the hemiplegia or hemianesthesia is accompanied by oculomotor palsy; and this oculomotor palsy will be on the other side of the body. As a rule, moreover, the paralysis of the third nerve which we find attending hemiplegia of peduncular origin is only a partial paralysis.

The fibers of the oculomotor which run out from the inner border of the peduncles of the cerebrum are derived from scattered groups of nerve cells which lie beneath and along side the third ventricle. These cell groups have a considerable fore-and-aft range, and it is easy to see that minute lesions (*e.g.*, cysts of softening) may produce various partial eye-muscle paralyses. Consequently in the region of the third ventricle we may have lesions producing certain characteristic clinical entities whose histopathological origin may in one case be inflammatory, in another case vascular, in a third case degenerative, in a fourth case due to tumor or parasite.

Wernicke's disease, *polioencephalitis hemorrhagica superior*, found in cases of alcoholism and in certain other intoxications, is clinically an ophthalmoplegia from the paralysis of eye muscles.

Above the nuclei of the eye muscles lie the *corpora quadrigemina*. We are certain that lesions of the anterior corpora quadrigemina produce disorder of vision. As to results of lesion limited to the posterior corpora quadrigemina we are not sure. The clinical rule is that " cerebellar " ataxia combined with bilateral paralysis of eye-muscles points to a disease of the quadrigeminal region. In a case of tumor of the pineal gland which effected pressure upon the quadrigeminal region the only demonstrable sign was stiffness of pupils. This sign, reflex rigidity of pupils, is otherwise found only in diseases of the tabetic and general paretic group.

If we mount upward from the peduncular region to the *internal capsule* we find conditions somewhat the same. In the knee of the capsule run the motor paths to the muscles of the head. In the anterior two-thirds of the posterior limb of the capsule run the paths to the muscles of the extremities and of the back (the arm path lies anterior to the leg path). In the posterior third of the posterior limb lie the sensory paths. Lesions of the internal capsule consequently produce total hemiplegia which may be combined with hemianesthesia if the area injures the posterior third.

What is the effect of lesion of the *basal ganglia?* If the internal capsule fails to show lesion, then paralysis and anesthesia are absent. In some cases of disease of the lenticular nuclei, abnormal movements of a *choreiform* or *ataxic* character have been observed. Unfortunately the same choreiform and ataxic movements are produced by any irritative lesion so localized as to compress the pyramidal tracts at any level. With respect to the optic thalami many persons suppose them related to the muscular movements of expression and maintain that lesion of the optic thalami will produce either absence of the mimetic movements in the case of destructive lesion, or alteration of them in the case of irritative lesion. We are sure that destruction of the pulvinar produces hemianopsia. Naturally, however, hemianopsia may be produced by lesions higher up than the pulvinar, and from a hemianopsia alone it will be impossible to conclude a lesion of the pulvinar.

Symptoms of Disease of the Cerebellum.

The cerebellum produces direct effects, not upon the senses or upon sensation, but rather upon muscular movements. Loss of the cerebellum produces incoördination of muscular movements, shown in standing and walking, and even in sitting. The patient stands with feet wide, sways, and is unsteady by reason of contractions of the extensors of feet and toes. The swaying of the back may prevent standing or even sitting without support. The swaying as a rule fails to increase on closing the eyes. The gait is drunken. The legs are more affected than the arms. Cerebellar ataxia fails to be exhibited in the performance of single movements, but occurs in attempts at combined movements. Cerebellar lesions produce not a genuine motor ataxia but a loss of the normal coöperation between back movements and limb movements (asynergy). The legs start forward without the back, or the head and back move without the legs. The lack of muscular coöperation may be unilateral and then as a rule depends upon a lesion of the cerebellar hemisphere on that side or upon a lesion of the restiform body or Deiters' nucleus. These so-called asynergies and hemiasynergies of cerebellar origin have been described by Babinski. Babinski thinks also that cerebellar lesions maintain or increase the capacity of the patient to hold his limbs in a fixed or cataleptic posture. The normal capacity to perform antagonistic movements (*e.g.*, pronation and supination) in rapid succession may be lost.

Lesions which affect the hemispheres alone may produce no symptoms. Irritative lesions of the hemispheres or brachium conjunctivum yield forced postures and forced movements, such as turning or falling to one side. Falling to one side is due as a rule to a destructive lesion. In cases of lesion of the restiform body the falling takes place to the side of the lesion. The direct or crossed hemiplegia attributed to cerebellar lesions is probably due to pressure upon the pyramidal tracts. Various motor irritative phenomena (general or unilateral convulsions, tremor, clonic contractions) ascribed to cerebellar lesions are probably better ascribed to irritation of neighboring motor structures or centripetal paths.

The characteristic results of cerebellar lesions are incoördination, vertigo, with perhaps speech-disorder and nystagmus.

The cerebellum receives impulses from the skin, the muscles, the joints, the semicircular canals, and other peripheral parts. These tracts, direct cerebellar, Gowers', posterior column-cerebellar, vestibular, central tegmental, olivocerebellar, run chiefly in the corpus restiforme. The cerebellum sends out impulses (hypothetically by way of brachium conjunctivum to pons and anterolateral ground bundles), by way of Deiters' nucleus through vestibulospinal tract to cord, and by way of superior peduncle through optic thalamus to the cerebrum. The cerebrum also contributes impulses to the cerebellum by way of a corticopontine path uniting the frontal lobes (where there are voluntary centers for the back muscles) with the opposite cerebellar hemisphere, which may act reflexly and automatically upon the movements.

The cerebellum is also put into relation with the oculomotor nuclei by way of Deiters' nucleus and the inferior longitudinal fasciculus.

The cerebellar cortex presents a uniform structure throughout with respect to the three constituent layers, the molecular layer, the layer of Purkinje cells, and the granular layer. The afferent or centripetal nerve fibers of the cerebellum terminate between the granule cells of the granular layer and in the molecular layer. The efferent or centrifugal nerve fibers originate in the larger cells of the cerebellum. With respect to the large cells of Purkinje it is doubtful whether they give rise directly to fibers which leave the cerebellum, or whether their fibers are thrown into connection with the rest of the nervous system by way of the dentate nucleus. The dentate nucleus and the nucleus of Deiters both receive and give rise to nerve fibers of the projection system.

If we conceive the cerebellum as a system of concentric reflex arcs and neglect for the moment the cross connections of these arcs and their relations with higher centers, we must take the ascending arms of the arcs to be as follows:

L. The direct cerebellar tract, running from Clarke's cell column by way of the restiform body to the neighborhood of the vermis.

2. The tract of Gowers (origin and particular ending in cerebellum unknown).

3. Fibers from the nucleus of the lateral tract.

4. Fibers from the opposite olive.

5. Fibers from the vestibular nerve, running to the nuclei of Deiters or of Bechterew.

The above tracts form an apparatus for the cerebellar registration of numerous data with respect to the position of the body and its parts. Thus through the direct cerebellar tract and the tract of Gowers (which may be together termed the long spino-cerebellar tracts) is effected the registration of the trunk muscle sensations. It is still in doubt what muscular regions (of the head or neck) get their cerebellar registration by way of the lateral tract nucleus and the olive. The vestibular connections probably effect the cerebellar registration of impulses from the semicircular canals.

The descending arms of the cerebellar reflex arcs are less precisely known. Fibers from the nucleus of Deiters descending to the anterior columns and fibers derived from Purkinje cells (or perhaps rather from the nucleus dentatus) and passing in the brachium pontis may be mentioned.

It is probable that many of the impulses derived from the trunk muscles and from the semicircular canals fail to be tallied forthwith in impulses sent directly downward. It is probable that the cerebral cortex and the centers of the mid-brain may be interposed before direct cerebellar response. The cerebellocortical paths are interrupted. The fibers run by way of the middle portion of the brachium pontis and by way of the brachium conjunctivum and end in gray nuclei of the mid-brain. The returning corticocerebellar paths are also interrupted.

The whole system of afferent and efferent fibers in the cerebellum, together with the plan of the cerebellar relations with higher centers, is still largely hypothetical. Three main cerebellar reflex arcs may be borne in mind.

1. Spinocerebellar reflex arc (Clarke's cell column, direct cerebellar tract, vermis, lateral tract nucleus, cerebellum or Deiters' nucleus directly to anterior column). This arc has to do with automatic equilibration movements and the coördinative movements which govern the static relations of the body.

2. Cerebellocortical reflex arc (cerebellum-mid-brain or optic thalami-cortex, by way of the tegmental portion of the brachium pontis). The returning fibers come by way of the frontopontine path. Their impulses are in part drained toward the cord, in part run back to the cerebellum.

3. Reflex arc of brachium conjunctivum and cortex and tegmentum (nucleus dentatus to red nucleus and optic thalami to cortex, cortex to subthalamic region and tegmentum to cerebellum).

FUNCTIONS OF THE CEREBRAL CORTEX.

In 1870 the dominant view of physiologists was that the cerebral hemispheres are not excitable by any known stimulus. To be sure, more than a century before, Haller and Zinn had observed convulsive movements upon injury of the white substance of the cerebrum. No one in the nineteenth century, however, had been able to procure similar results. The most frequently cited work was that of Flourens. The extirpations of Flourens seemed to prove that the hemispheres were the seat of the will and of sensation but had nothing directly to do with motion. Flourens had also concluded that the cerebral tissue acts as a unit in effecting reactions and that, upon excision of portions the remainder will, to a certain limit, take over this total function (much as we now suppose a portion of the thyroid gland will serve for the whole).

Hitzig, however, was able to bring forward observations which cut under much of Flourens' theory.

Hitzig had an opportunity to observe in man contractions of voluntary muscles following direct electrical irritation of the brain. The movements observed were eye-movements and followed galvanic irritation of the back of the head. In point of fact the resulting movements are due to irritation of the vestibular nerves. Nevertheless, Hitzig was led by this actually erroneous interpretation to try electrical irritation of the rabbit's cortex. The result encouraged him to undertake with Fritsch decisive experiments on the dog. It was shortly found that a portion of the dog's cerebrum is motor, a portion not motor, the motor part lying forward of the non-motor part. Electrical irritation of the motor portion produced combined contractions in the opposite half of the body. Upon application of weak currents certain definite small groups of muscles were stimulated, whereas with stronger currents other muscles, and even muscles on the stimulated side of the body, were also involved. Isolated contraction of a certain muscle group was produced by a current of minimal strength applied to a small focus, called by Hitzig a center. By shifting the electrode slightly, the contraction might be changed in character, say from extension to flexion or rotation. The intervals between the centers were found inexcitable, that is, inexcitable with the strengths of current used to demonstrate the center; upon increase of current, contractions of generalized character set in.

Hitzig was able to demonstrate centers for neck-muscles (lateral portion of prefrontal convolution), for extensors and adductors of fore-leg (external to tip of frontal fissure), for flexors and rotators of fore-leg and for hind-leg (posterior to above), and for the facial (middle portion of the second primary gyrus of Owen's nomenclature). He was unable to demonstrate isolated centers for the central innervation of the back, tail, and belly muscles. Posterior to the facialis center the cortex proved inexcitable even with a current of ten Daniell cells.

The character of current employed was found to modify resulting contractions just as in the case of peripheral nerves, save that there was a constant predominance of the anode. Using currents of the minimal strength adequate to produce contractions Hitzig found that only the anode would effect contraction.

Induction currents were found not so constant in effect. Continued movements rather than isolated contractions often followed, thus tremor in the facialis region, clonic contractions in the limbs, occasionally epileptic attacks.

Hemorrhage speedily lowers the cortical irritability and, immediately after death while the muscles and nerves are still irritable, the strongest currents are unable to produce movements by way of the cortex.

Hitzig concluded that he had proved a reaction on the part of certain central structures to artificial stimuli, a reaction in the form of muscular movement upon stimulation of nerve tissue comprising almost half the hemispheres. He notes that similar reactions had before been suspected by anatomists, notably by Meynert, but that no intracranial structures had hitherto been proved so to respond, except certain basal structures, the thalamus, the pons, and the like.

But the interpretation was not so clear. That electrical stimulation of a center produces a muscular contraction is no proof that the center is *the* voluntary center for the muscle group involved. The electrically excitable centers may be intermediary bits of apparatus, mere filters for impulses from elsewhere.

We may, however, prove, by means of needles partly incased in gutta percha and introduced into the subcortical white matter, that the fibers there are stimulable. Probably, then, Hitzig reasons, they continue stimulable in their course within the gray matter as far as the cells with which they unite.

We know much more about the effect of lesions of the cortex upon functions than we do about the effect of deeper lesions. The cortex is more accessible to experimental work and since the work of Fritsch and Hitzig in 1870 upon cerebral localization, we have learned much concerning particularly the motor centers. With respect to the relation of the cortex to consciousness we are sure of a general correlation, but to this day we have no further remarks concerning the especial localization of processes underlying the mental life than to say that the frontal lobes are probably particularly concerned with the higher mental processes.

The motor region consists of the precentral convolution and its continuation upon the mesial surface of the brain. The upper part of the precentral convolution and its mesial continuation is related with the leg movements, the middle portion to arm movements, and the inferior portions to the movements of the face and tongue. If we irritate but do not destroy a center, we produce contraction of the muscles controlled. If the stimulus lasts, the irritations are propagated to the other centers on the same side, and then to the opposite side of the brain, that is to say, local spasm becomes a hemispasm and then a total spasm.

Since the fundamental work of Fritsch and Hitzig upon the electrical excitability of the cerebral cortex, much has been done in the field of cortical localization. The data from electrical excitation are nearly complete, although the significance of the frontal lobe, the cortical representation of the back muscles, certain details in the cortical representation of the extremities and of the facialis region, and the interpretation of the results of stimulating the occipital region, remain to be cleared up.

The *motor area* is roughly coincident with the precentral (ascending frontal) gyrus in man and corresponds to the region in which the large cells of Betz are found. The region includes the adjacent part of the paracentral lobule and stops abruptly behind with the floor of the Rolandic fissure. The Betz cells fail to occur in two parts of this area, namely, in the region of the superior genu and near the lower extremity of the Rolandic fissure. The largest Betz cells are found in that part of the paracentral lobule which is adjacent to the precentral gyrus; these cells control the movements of the foot and lower leg. The Betz cells of the precentral gyrus in its upper part (down to the region of the superior genu) control the movements of the thigh and buttock. The region free of Betz cells just above the superior genu (the deep annectent gyrus of the Rolandic fissure) is related with trunk movements. Below the superior genu the precentral gyrus begins again to show large cells; these control the shoulder, arm, and neck. The lower part of the precentral gyrus, destitute of large cells, is related with the muscles supplied by the facial nerve.

The cortical representation of the sense of *sight* is in the occipital region in the gyri bounding the calcarine fissure and is probably related with the distribution of the white line of Gennari which is visible in that region on gross inspection. The calcarine region of the left hemisphere is directly related with the sight of the left halves of both eyes; destruction of this region produces homonymous hemianopsia. That portion of the occipital cortex which surrounds the calcarine region is probably related with the elaboration and interpretation of visual sensations.

The cortical representation of the sense of *hearing* is in the superior temporal gyrus. The portion of this gyrus which is concealed within the Sylvian fossa bears several transverse elevations — the transverse temporal gyri of Heschl. These transverse temporal gyri are probably related with the cortical reception of *immediate* auditory stimuli. The elaboration and interpretation of these stimuli is probably a function of the exposed flank of the posterior three-fifths of the first temporal gyrus.

The cortical representation of the senses of touch, pressure, pain, and temperature, that is, of *common sensation*, is in the region of the postcentral (ascending parietal) gyrus. The elaboration and interpretation of these stimuli is probably a function of the cortex posterior to the postcentral gyrus, viz., of the superior parietal lobule. The elaboration of these common sensory data yields our sense of the position and condition of muscles (*muscle sense*) and our appreciation of the shape and consistence of objects (*stereognosis*).

The cortical representation of the sense of *smell* is probably in the region of the *lobus pyriformis*, a part of the hippocampal gyrus. The wall and lip of the hippocampal fissure may perhaps be concerned with elaboration of olfactory stimuli.

The cortical representation of the sense of smell is possibly to be assigned to the island of Reil.

The cortical representation or origin of the higher and specialized movements belongs to the intermediate precentral, frontal, and prefrontal areas. The prefrontal area is an area poor in nerve fibers and in nerve cells, and may perhaps be regarded as phylogenetically of recent development. The cortical representation of the higher *intellectual faculties* is plausibly assigned to the frontal area. This area occupies, upon the lateral surface of the hemisphere, the anterior half of the superior frontal gyrus, a portion of the middle frontal gyrus, and the tip of the inferior frontal gyrus; upon the mesial surface of the hemisphere, a part of the marginal gyrus above the genu of the corpus callosum;

and upon the orbital surface of the hemisphere, a small portion external to the external sagittal sulcus.

The cortical representation of certain skilled movements, such as speech and writing, may be placed in the intermediate precentral area. This area covers the base of the superior and middle frontal gyri, a small part of the precentral gyrus, and much of the inferior frontal gyrus including on the left side the so-called pars basilaris or area of Broca.

Wernicke has maintained that mental diseases are brain diseases. Evidently they are not focal brain diseases but general ones. The mental diseases may be aligned with meningitis and with general paresis as a third kind of general brain disease, clinically distinguished from the former two by the absence of focal symptoms. Mental diseases may, therefore, be defined as general brain diseases which are not attended by focal symptoms.

Focal symptoms are due to interruption or irritation of foci in the projection system or of foci at the cortical end-stations of the projection system. The cortical end-stations are not precise equivalents of the lower parts of the projection system. The end-stations are the site of memory-images as well as of the immediate peripheral arrangements of sensation and motion. The losses of the various kinds of image may also be counted among focal symptoms. The mental diseases are once more distinguished from meningitis and general paresis by the absence of focal symptoms, not merely those due to disease of the projection system, but also those due to disease of certain parts of the cortex. It is not exact to say that mental diseases are cortical diseases.

Even if we conceived that the whole of the cortex is an array of end-stations for the projection system, we should not be at a loss in the localization of mental diseases. Mental diseases are in fact particular diseases of the association organ formed by the fibers which unite the cortical end-stations of the projection system.

The value of assuming a concept center is seen when it is considered how the word-image has, not merely to be recognized as such, but also to be understood. If the recognition at the cortical projection field be termed primary identification, the understanding may be termed secondary identification. The cortical projection field for sensory speech is the office from which the message is forwarded to the true receiver of the message at the concept center. Whence again the message passes to the dispatching office at the motor speech center.

Mental diseases and some cases of aphasia have in common a disorder of secondary identification, a process localized in the association system. Mental diseases must be essentially transcortical.

To prove such a structural conception of mental diseases right or wrong is the immediate neuropathological task. It is probable that structural changes in the synapses of elaborating centers (such as the flank of the superior temporal gyrus or the occipital region at large) will mean as much in future work as the association fiber changes hypothecated by Wernicke.

IV. NUMERICAL DATA.

Average weight of male adult brain	1,358 gms.
Average weight of female adult brain	1,235 gms.

Methods of taking weights vary. Sometimes the pia mater is included: this weighs from 25 to 40 grams. The amount of intracranial and ventricular fluid is said to vary from 41 to 103 grams under normal conditions.

The average weights given above are for the brains of adult Europeans.

Average weight of male brain at birth	381 gms.
Average weight of female brain at birth	384.2 gms.

This slight excess of weight in the female brain at birth is analogous with a similar slight excess in several other major organs of the female. The liver at birth, *e.g.*, is assigned the weight 100.5 grams in the male against 164 grams in the female. The differences are gradually made up.

Average weight of male brain at one year	944.7 gms.
Average weight of female brain at one year	872 gms.

The male brain begins to weigh over 1,200 grams during the fourth year, the female brain not till the sixth year. After this period the majority of observations indicate that the male brain remains a little heavier than the female brain.

Specific gravity of gray matter	1.0313
white matter	1.0363
cerebrum as a whole	1.0361
cerebellum	1.0321
cord	1.0343
calvarium	1.717
striated muscle	1.0414

WEIGHTS OF BRAIN PARTS.

The percentages of weight shown by its various parts of the cerebrum are approximately:

Frontal lobes	29
Parietal lobes	37
Occipital lobes	10
Temporal lobes	14
Insula and lobes at base	10

The weight of the cerebellum is about 12.8 per cent of the total brain weight, and is variously given 159 to 169 grams.

Midbrain	26 gms.
Pons and bulb	28 gms.

DEPTH OF CEREBRAL CORTEX.

Male.		Female.	
Right	Left	Right	Left
Hemisphere.		Hemisphere.	
2.91	2.94	2.89	2.92

The average depth as given is 2.94 for males, 2.92 for females.

DEPTH OF CALVARIUM.

At occipital protuberance	15 mm.
At vertex	5–7 mm.
In squamous portion of temporal bone	2 mm.
Average	3–4 mm.

CRANIAL INDICES.

The distance between the glabella and the external occipital protuberance is the technical *length* of the skull, the usual length is 20 centimeters in males, 18 centimeters in females, 12 centimeters at birth in both sexes.

The maximal breadth is the technical *breadth* used in determining skull indices. The average breadth is 14.6 centimeters.

The *length-breadth index* is obtained by multiplying the breadth into 100 and dividing by the length. Thus

$$\frac{100 \times \text{breadth}}{\text{length}} = e.g., \frac{100 \times 14.6}{19} = 76.8$$

The accepted classification of skulls according to the length-breadth index is as follows:

Skulls.		Index.	
Dolichocephalic	1.	55.5–59.9	extreme dolichocephaly.
	2.	60.0–64.9	ultradolichocephaly.
	3.	65.0–69.9	hyperdolichocephaly.
	4.	70.0–74.9	dolichocephaly.
Mesocephalic	5.	75.0–79.9	
Brachycephalic	6.	80.0–84.9	brachycephaly.
	7.	85.0–89.9	hyperbrachycephaly.
	8.	90.0–94.9	ultrabrachycephaly.
	9.	95.0–99.9	extreme brachycephaly.

In taking measurements in the living, the presence of the soft parts about the skull must be considered. These may raise the length-breadth index two or three units. The length-breadth index averages about 80.

CUBIC CAPACITY OF CRANIA.

The cranial capacity increases from 380 to 450 cubic centimeters in the new born to 700 to 1,000 cubic centimeters at the end of the first year, and later to about 1,300 cubic centimeters in the tenth year. The following classification of skulls according to cubic capacity has been adopted for adults:

Nannocephalic	under 1,300 ccm.
Emmetrocephalic	1,300–1,400 ccm.
Encephalic	1,500–1,699 ccm.
Megalocephalic	1,700 + ccm.

MEASUREMENTS OF SPINAL CORD.

Length.	Males.	Females.
Cervical	9.9 cm.	10.0 cm.
Thoracic	26.2 cm.	22.9 cm.

Length.	Males.	Females.
Lumbar	5.1 cm.	5.7 cm.
Sacral	3.6 cm.	3.1 cm.
Depth	0.9 cm.	
Breadth	1.0–1.1 cm.	
Cervical swelling	1.4 cm.	
Lumbar swelling	1.2 cm.	

V. REFERENCES.

Following is a list of books upon which the present outline has been in part based:

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A Study of Acute Leptomeningitis
(Streptococcus Pyogenes.)

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AND

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BOSTON.

Reprinted from The Journal of the American Medical Association, October 20, 1906, Vol. xlvii, pp. 1271-1277.

CHICAGO:
PRESS OF THE AMERICAN MEDICAL ASSOCIATION,
ONE HUNDRED AND THREE DEARBORN AVENUE,
1906.

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A STUDY OF ACUTE LEPTOMENINGITIS (*STREPTOCOCCUS PYOGENES*).*

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The present report comprises a series of human brain infections with *Streptococcus pyogenes*, together with the results of experimental inoculation of streptococci in the brains of guinea-pigs. The human cases have been studied histologically with particular reference to, first, the age of the exudations; secondly, certain prominent vascular lesions; thirdly, the neuroglia reaction. The guinea-pig tissues are of value mainly in the study of the exudation. The work has been carried on with methods like those employed in two previous studies, on infections with *Staphylococcus pyogenes aureus*[1] and with pneumococcus.[2]

We have little evidence to bring on the vexed question of the relationship of pneumococcus and streptococcus. The lesions reported here differ in no constant feature from those reported by Southard and Keene in 1905 for the pneumococcus.[2] The effects of the two organisms on tissues, so far as observable by the methods used, would place the organisms in one group.

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*From the pathologic laboratories of the Boston City and the Danvers Insane Hospitals.

* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

[1] Southard, E. E., and Keene, C. W.: "A Study of Acute Hemorrhagic Encephalitis (*Staphylococcus pyogenes aureus*)," Am. Jour. Med. Sci., March, 1905.

[2] Southard, E. E., and Keene, C. W.: "A Study of Brain Infections with the Pneumococcus," THE JOURNAL, vol. xlvi, Jan. 6, 1906, p. 13.

We are under obligations to Professors Councilman and Mallory for direction of the work, to the various members of the City Hospital and the Danvers Insane Hospital staffs, named below, for the clinical sketches, to Dr. E. E. Tyzzer for his private case, and in particular to Drs. C. W. Duval and P. A. Lewis for supplying us with cultures in the course of their pneumococcus work in 1904-5.[3]

CASE 1.—G. K., male, aged 35, was admitted to Dr. J. Orne Green's aural service at the Boston City Hospital, March 31, 1900.

Clinical History.—Patient had had four attacks of chills and fever in past two years. Two weeks before admission there had been headache, malaise, severe pain in both ears, followed by bloody discharge two days later, and by a chill two days later. Pain in vertex of skull a little to right of median line, restlessness, insomnia, vomiting. Night before entrance, rigor for five minutes, followed by sweating, temperature 104. Both tympana were found perforated and remains of drum swollen. Tongue was coated and tremulous. Temperature rose to 103 and 105 and remained high during the day following. Leucocytes 16,000, April 5. Mastoid exploration: *Streptococcus pyogenes.* Improvement in headache, temperature 103. April 8, temperature 105.5, leucocytes 8,000. April 10, delirium, dilatation of pupils, vomiting, hiccough. April 11, muttering delirium, almost constant hiccough, fixed and dilated pupils, fibrillary tremor of neck and arm muscles, retraction and rigidity of neck. Death, April 12. Arms rigid four hours before death.

Autopsy Findings.—The autopsy, performed 10 hours after death by Dr. Fulton, gave the following head findings, with abstract of trunk findings: Calvarium normal. Sinuses normal. Dura slightly more tense than normal. Subdural space dry. Convolutions flattened. Scattered over the cortex are a few small yellowish opaque areas (2 to 3 mm. in diameter) set, as a rule, along blood vessels of the sulci. The material in these areas is tough and tenacious. The largest area (about 1 cm. in diameter) is on the mesial surface of the left frontal lobe. Yellowish-white fibrinopurulent exudate covers optic chiasm, optic tracts near chiasm, the cranial nerves, the under surface of pons and medulla, the superior vermis of the cerebellum. The exudate does not communicate with the auditory meatus. The ventricles contain from 30 to 50 c.c. of cloudy gray fluid and a small amount of pus in each posterior cornu. Choroid plexus is swollen and grayish. There is pus in lateral recesses of fourth ventricle. Mastoid operation in right ear. Left middle ear contains a slight amount of serous fluid.

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[3] Duval, C. W., and Lewis, P. A.: "Studies on the Pneumococcus," Jour. Exper. Med., vol. vii, No. 5, August, 1905.

Anatomic Diagnosis.—Acute leptomeningitis, encephalitis, and ependymitis. Mastoid operation (right side). Acute splenic tumor. Decubitus of right buttock. Echinococcus cyst of liver. Slight endaortitis. Chronic fibrous pleuritis.

Microscopic Findings.—Cultures from cortex, optic nerve, ventricles and lung gave *Streptococcus pyogenes.* Cultures from heart, spleen and liver were sterile, from kidney negative.

The cortex shows a deep meningeal exudate in which the phagocytic cells far outnumber the other types. The distribution of cells is irregular, since in a few foci about veins there are dense groups of lymphocytes. In a very few places there are fields with polynuclear leucocytes predominating. Vascular lesions are not prominent. The cortical tissue shows little evidence of lesion other than a swelling of the neuroglia cell bodies of the subpial layer. There is no evidence of multiplication of these cells.

The acute inflammation of the lining of the ventricle is shown by a diffuse infiltration with polynuclear leucocytes and an almost universal diffuse swelling of neuroglia cell bodies. The ependyma appears in places as a double or triple row of irregularly arranged cells. Among the ependymal cells is an occasional leucocyte.

The choroid plexus shows an exudate both within and between the folds. Connective tissue cells about the vessels within the folds are swollen. In places there is a dissection of the epithelial cells away from central fibrous tissue by means of polynuclear leucocytes. The vacuoles of the epithelial cells are often perfectly demonstrated, even in folds packed with leucocytes. Of the cells outside the epithelium, the majority are polynuclear leucocytes, mixed with desquamated epithelial cells and a limited number of cells of the phagocytic series. There are few cells of the lymphocyte series.

The cord shows a meningeal exudate in which polynuclear leucocytes are still numerous, but are outnumbered both by phagocytic cells and by cells of the lymphocyte series. In some places the lymphocytes exceeded the phagocytic cells in number. Cells of the plasma cell type stand out prominently, especially when they contain two or three nuclei. The phagocytic cells contain both fat and exudative cells. Of the included cells, lymphocytes and plasma cells are the most prominent; but polynuclear cells are also seen; and it was not rare to find cells of all three kinds engulfed in a single phagocyte. Some of the plasma cells escape inclusion and undergo a spongy vacuolation of the cell-body, which remains basophilic very late, together with a swelling of nucleus and clumping of chromatin.

At the points of deepest exudate the vessels have undergone extensive local lesions. All three coats of the arteries may be involved; the adventitia shares in the general meningeal exudate, emigrating leucocytes may be found sometimes in the muscularis, and the intima is often lifted by exudate cells. There are more polynuclear cells and deposits of fibrin about the arterial lesions than elsewhere. In the walls of the veins polynuclear cells and particularly plasma cells are prominent.

Case 2.—J. D., male, aged 49, was admitted to Dr. J. Orne Green's aural service at the Boston City Hospital, May 30, 1900.

Clinical History.—Patient had had pneumonia at 30. There had been severe headache and a discharge from right ear for three weeks. On admission ear showed slight infiltration of membrana tympani and looked convalescent. There was drowsiness and severe headache. Heart was enlarged to left. Arteriosclerosis. May 31, pain also in back and hips, increasing stupor, followed by unconsciousness at noon. Retention. Bloody urine drawn by catheter. Death, June 1, in coma with slight rigidity of extremities and moderate dilatation of pupils.

Autopsy Findings.—The autopsy, performed 54 hours after death by Dr. H. C. Low, gave the following head findings, including an abstract of the trunk findings:

Dura is only slightly adherent to calvarium. Vessels of dura are considerably injected. There is no sign of thrombus in any of the sinuses and no edema. Vessels of pia are considerably injected. There are few slight subpial hemorrhages over vertex. Near vertex, more especially near the posterior part, there is a fair amount of purulent secretion, and over the top of the cerebellum, between the posterior parts of the hemispheres and over nearly the whole of the base of the brain, there is considerable thick purulent exudation. On the under side of the right temporal lobe is a small place nearly 1 cm. in area where the cortex and meninges are adherent to the base of the skull. At this point a little pus came from the brain tissue. On cross section through both hemispheres at this point there is exposed in the right temporal lobe an abscess cavity about 3 x 3 x 4 cm. This is filled with thick yellow pus. About this for an area of from 1 to 2 cm. the brain tissue is soft and reddish and numerous dark red points fill nearly the whole of the rest of this lobe. No other abscesses are found in the brain tissue. In the ventricles there is a fair amount of thick purulent secretion which covers the choroid plexus.

Both middle ears are normal. The point where the brain and meninges are adherent to the skull is near the center of the right middle fossa just anterior to the eminence of the semicircular canals, and on chiseling away the bone from here, pus is found to be in some of the bone spaces. Just posterior to this, but a little more to the side, for nearly over the entire end of the external canal there is a slight amount of pus in the bone spaces. Mastoid cells have been scraped out in operation. Mastoid cells anterior to field of operation do not appear to be subject to any suppurative process.

Anatomic Diagnoses.—Acute leptomeningitis and ependymitis. Abscess of right temporal lobe. Suppurative osteitis of petrous portion of right temporal bone. Mastoid operation. Acute hemorrhagic cystitis. Healed pulmonary tuberculosis with localized tuberculous pleuritis. Chronic fibrous pleuritis. Slight chronic interstitial nephritis. Hypertrophy and dilatation of heart. Slight area of fatty change in mitral valve.

Microscopic Findings.—Culture from lateral ventricle gave *Streptococcus pyogenes.* The brain abscess contained a variety of organisms. Cultures from heart's blood, spleen, liver and kidney were sterile.

The histologic changes in the cortex are chiefly related to the underlying abscess. The meningeal exudate is slight and composed of mononuclear cells, mixed with a few polynuclear leucocytes. The mononuclear cells, as a rule, approach the plasma cell type. Compressed plasma cells sometimes occur singly or in pairs in the walls of small vessels in the nerve-cell layers of the cortex. For the most part there is very little sign of exudate in the deeper layers. The cells about the smaller vessels near the abscess are swollen and increased in number. Cells in apposition with the vessel walls are occasionally seen in mitosis. The nerve cells have undergone a variety of changes which are chiefly the product of edema—swelling and vacuolation, shrinkage and chromophilia, extrusion of nucleolus. The satellite cells occur often in groups of eight or ten, about the small pyramidal nerve cells, which are themselves, as a rule, in some degree altered. The satellite cells fail to show well-defined cell bodies or any sign of inclusions. There seems to be evidence that nerve cells may occasionally disappear from the midst of satellite cell groups. No mitoses were observed among the satellite cells in this case. Near the abscess there are a few nuclear figures in large cells, some of which had numerous vacuoles in their cell bodies outside the spindles. It is doubtful whether these figures occur in endothelial or neuroglia cells. There is little evidence of cell cavity. In the areas of frank hemorrhage here and there is a phagocytic cell containing blood globules.

The lining of the ventricle is macerated. There is rarely any evidence of proliferation in the lining cells. In places the wall is supplanted by masses of fibrin containing exudative cells. The vessels of the underlying tissue are dilated, sometimes to an unusual degree, and the sheaths of the veins are filled with cells of the lymphocyte series, including many examples of the plasma cell. Mitotic figures are scattered at rare intervals through the edematous tissue underlying stripped portions of the ventricular lining. One skein form was found in a highly vacuolated cell which lay free in a collection of blood globules. Otherwise the tissue shows merely degeneration or necrosis. In some cases the small cells near the nerve cells share their chromophilia, but in other cases the small cells appear to stain densely at a stage when the nerve cells are still fairly well preserved. The tissue under the ventricle appears to have been more directly subject to injury than the tissues about the subcortical abscess, so that there is here more sign of degeneration than of the cell proliferation seen about the abscess.

Case 3.—R. R., male, aged 53, was admitted to the service of Dr. A. L. Mason at the Boston City Hospital, April 21, 1901.

Clinical History.—Patient had been in bed three weeks before admission; malaise, weakness, headache, dizziness. On admission cheeks were flushed, slight left internal strabismus, pupils small; otherwise all signs were negative. The day after admission temperature rose to 102, patient became restless and noisy and tremor of extremities set in. April 24, ascites, dribbling of urine, mild delirium, Cheyne-Stokes respiration. April 26, incontinence of feces, rigidity of neck. April 29, patient unconscious and quiet, respiration rapid and superficial. Death.

Autopsy.—The autopsy, performed by Dr. E. E. Southard twenty hours after death, showed:

Head: Calvarium and dura normal. Longitudinal sinus filled with dark fluid blood. Subdural space shows marked increase of fluid; probably 300 c.c. leaks away. Pial vessels injected, pia over sulci opaque and tense from contained fluid. There is considerable web-like, thinly-spread opaque connective tissue in basilar region, especially around optic chiasm and in Sylvian fossæ. Brain substance is very soft; corpus callosum like Neufchatel cheese. All tissues are moist. Puncta cruenta distinct on section of centrum semiovale. There is about a test-tubeful of clear fluid in each lateral ventricle.

Cord: Much clear fluid under tense dura. Cord tissue is firm and well shaped, but over all is a thin, glistening, opaque-white deposit, slightly more marked in lumbar region. Foramen of Magendie and accessory foramina are occluded by this overgrowth. Middle ears normal.

Anatomic Diagnoses.—Basilar and spinal organizing meningitis. Internal hydrocephalus. Increase of subdural fluid. Edema of brain. Fatty degeneration of heart muscle. Slight fatty degeneration of renal epithelium. Congestion of spleen, liver, kidney, pancreas, bladder mucosa. Chronic pharyngitis. Hypostatic pneumonia. Chronic adhesive pleuritis. Chronic perisplenitis. Chronic interstitial orchitis.

Microscopic Findings. — Cultures from heart's blood and lung showed *Streptococcus pyogenes* and many other organisms. The liver showed *B. coli.* The tissues at the base show considerable variety in exudate. The looser tissues contain fibrin and polynuclear leucocytes, which outnumber the other kinds of cell. The adventitiæ of the vessels contain numerous cells of the lymphocyte series.

Intimal lesions, although prominent in arteries of smaller caliber, spare the larger arteries. The intimæ of the smaller arteries are lifted or completely dissected off by an exudate composed chiefly of cells of the lymphocyte series, among which are examples of the typical plasma cell. Between the loosened intima and the elastic layer of the artery there may be deposited a dense, deeply-stained sheet of fibrin. In late stages of the lesion, when the intima has scaled off, the appearances simulate a fibrinous transformation of the intima. The smaller vessels are often wholly blocked by masses of fibrin and desquamated cells. The nerve tissue beneath the exudate is edematous and shows nerve cells in various stages of injury, retaining, as a rule, well-staining nuclei. Single leucocytes invade the pons tissue for several millimeters. There are a few narrow marginal areas of nerve tissue replaced by fibrin and leucocytes. The cord shows an exudate of cells of the lymphocyte series and well-developed vascular lesions resembling those at the base of the brain.

Case 4.—H. W., male, aged 31, was admitted to the service of Dr. Henry Jackson at the Boston City Hospital, July 30, 1903.

Clinical History.—There had been persistent emesis without gastric pain or distress, three weeks. Dizziness, frontal headache, blurring of vision, swelling of feet and ankles, slight cough with expectoration. Stopped work two days before admission. Urine contained albumin and casts. Diagnosis, chronic interstitial nephritis. Discharged four days after admission. Readmitted Sept. 10, 1903. Heart enlarged; soft systolic murmur at apex transmitted to axilla. Heart and kidney signs grew gradually worse. Mind not clear. Oct. 14, 1903, erysipelas set in; developed rapidly to sloughing of eyelids with severe chills. Death Oct. 15, 1903.

Autopsy Findings.—The autopsy, performed five hours after death by Drs. R. E. Lee and E. E. Southard, showed:

Head (Dr. E. E. Southard): Scalp is everywhere edematous, ranging from 2 to 3 cm. in thickness. Tissues over frontal eminence and orbits are brawny and hard to turn back. Calvarium of normal thickness, without diploë. Dura of normal tenseness and thickness. Moderate injection of middle meningeal system. Sinuses filled with fluid blood and cruor clot. Meshes of pia distended with cloudy (fibrinous) fluid, without cellular exudate. Arachnoidal villi moderately well developed. Substance moist. Ventricles showed no increase of fluid. Interbrain, midbrain and bulb normal. Vessels at base normal.

Middle Ears: Right normal. Left contains greenish fluid pus with streptococci. Ethmoid cells normal. Orbital tissues are infiltrated with greenish pus containing streptococci. Eyes removed from behind show fairly clear conjunctivæ, with impression of opacity behind, especially marked in left eye.

Anatomic Diagnoses. — Chronic diffuse nephritis. Hypertrophy of heart. Slight fatty myocarditis. Erysipelas of face. Acute purulent conjunctivitis. Edema of pia and of substance of brain. Acute otitis media (*streptococcus*).

Purulent infiltration of orbits (*streptococcus*). Slight bronchopneumonia. Chronic obliterative pleuritis (left). Fatty liver. Edema of glottis. Hydrothorax.

Microscopic Findings.—The exudate into the pial tissues consists of slight edema with exudative cells almost invariably mononuclear, mainly lymphocytes. There is an occasional polynuclear leucocyte. The only signs which can be connected probably with the septicemia are in some of the small arteries. These show desquamation of endothelium, with dense fibrin deposits on the elastica. The elastica in these arteries, which are in certain cases entirely plugged by leucocytic thrombi, fail to contract in the usual wave form, but remain smooth and flat. There is no considerable neuroglia reaction in the subpial layer or elsewhere.

Case 5.—J. B., male, aged 19, was admitted to Dr. G. A. Leland's service at the Boston City Hospital, Dec. 30, 1903.

Clinical History. — Patient had had measles as a child. There had been discharge from right ear for six years, with occasional attacks of pain and fever. External abscess once opened by family physician. Two weeks before admission a similar attack was followed by severe, continuous, generalized headache. Temperature 102 two days before entrance. Pain localized in occipital region, radiating to interscapular region. Neck rigid. Leucocytes, 24,000. Right mastoid operation (Dr. Leland). Temperature dropped to 100. Leucocytes, 16,000. Slight rotary nystagmus, more marked in right eye. January 1: Right facial paralysis. January 3: Pupils dilated, right more than left; fundus examination showed haze of both discs with congestion of lamina cribrosa and venous engorgement. Vomiting. Restlessness. Second operation by Dr. Leland; exploration of cerebellum. Apparent improvement. Vomited once. Pain in occiput allayed by morphia. Wound dressed under primary ether, January 5. Afterward delirious, crying with pain in head. Morphia. Delirium once more, followed by coma, morning of January 6; respirations 6 to 8; pulse not countable and intermittent. Death.

Autopsy Findings.—Examination, limited to the head, made by Dr. E. E. Southard 2¼ hours after death; showed scalp veins filled with fluid blood. Tissues adjacent to lips of wound gray and chocolate-brown, edematous and friable. The necrosis involves the mastoid insertions of the right sternomastoid, splenius capitis, and trachelomastoid muscles: head drawn forcibly to the left. Rigor absent. Tissues warm.

Calvarium thin, rarely reaching .5 cm. Right temporal bone removed intact by sawing shows thumb-sized cavity of the mastoid exenteration and perforations made for exploration of posterior fossa cerebri (cerebellum and temporosphenoidal lobe).

Dura of the usual thickness, lightly adherent opposite bregma, can not be picked up readily with forceps. Small perforations are found in outer portion of right posterior fossa cerebri. Localized on dura covering posterior surface of petrous portion of temporal bone, involving meatus internus and aqueductus vestibuli, is a layer, .2 to .4 cm. deep, of granulation tissue with thick fibrinous greenish-gray pus. Sinuses contain fluid blood. Tissues about right superior petrosal sinus soaked in pus.

Pia shows moderate injection, chiefly of the large veins of sulci, over vertex and sides. Meshes of pia under interbrain floor are filled with tenacious greenish pus which follows both Sylvian arteries for a few centimeters into fossæ Sylvii and follows anterior choroid arteries for some distance. Optic nerves are held in edematous purulent fibrous tissue; nerves look redder than usual on section. Slender processes of fibrin containing pus enclose anterior communicating and anterior cerebral arteries; leaves of pia in this region are somewhat firmly united. Pituitary not grossly involved. Pia over pons is distended with plastic layer of greenish pus. Considerable clear fluid is found between pia and dura. Pia over cerebellum contains no pus except immediately over abscesses, but the subdural space of the right posterior fossa contains considerable purulent fluid.

Ventricles: The posterior horns of both lateral ventricles, the anterior horn of right lateral ventricle and floor of third ventricle contain slight plastic deposits of greenish pus and fibrin, apparently settled out of a considerable surplus of turbid brownish fluid distending the cavities. The ependyma of the ventricles is swollen, deeply velvety and peels away in a clinging layer .1 to .2 cm. thick. Fourth ventricle is lined with what resembles an early pyogenic membrane, which can be peeled away readily, leaving an edematous ependyma with deep red punctation.

Substance: Sulci of hemispheres are almost effaced. Substance is moist. Very little injection either of cortical or of central ganglionic vascular systems. The substance of the right cerebellar hemisphere external to flocculus contains a greenish abscess cavity 2 x 2 cm. across, of an indefinite depth. The edema and a slightly greenish color invade the dentate nucleus playing out vaguely. Injected tracks of director (used for exploration) are found in cerebellum and temporosphenoidal lobe. The abscess is just missed by the exploration. Interbrain, midbrain, and isthmus are normal on section. Weight (minus considerable fluid) 1490 gm.

Anatomic Diagnoses.—Mastoid operation. Exploration of cerebellum and temporosphenoidal lobe. Chronic otitis media. Abscess of cerebellum. Acute fibrinopurulent basal leptomeningitis. Pyocephalus internus. Edema of substance with flattening of gyri.

Microscopic Findings.—Culture from brain showed streptococci.

The cortical meninges at the vertex show a thin layer of large mononuclear cells of the phagocytic type. One of these occasionally contains a polynuclear leucocyte.

At the base the exudate is often 3 to 4 mm. thick and varies according to its relation with vessels. The free exudate shows numerous cells of the phagocytic series, together with polynuclear leucocytes and cells of the lymphocyte series in about equal numbers. The adventitiæ of the veins contain chiefly cells of the lymphocyte series. The tissue at the base is the only region examined in this case which shows marked lymphocyte infiltration.

The cerebellum shows an exudate which is deepest in the sulci between the outermost laminæ and beneath the superficial pia mater. There is focal invasion of the molecular layer by leucocytes, either singly or in very small groups; but, beyond there, there is no evidence of either gross or selective injury to the nerve tissue. The exudate shows polynuclear leucocytes very prominently; but counting shows that they rarely exceeded the mononuclear exudative cells in number. Of these mononuclear cells the most prominent are large cells with eccentric vesicular nuclei, which are phagocytic for polynuclear leucocytes. About a few small veins are collections of cells of the lymphocyte series; for these cells the larger mononuclear cells fail to be phagocytic, save in rare instances.

The choroid plexus shows numerous cystic spaces about the larger vessels. The spaces contain granular material and numerous corpora amylacea. The acute inflammatory reaction fails to involve the central regions of the plexus, but is strikingly shown immediately below the ependyma in many folds. The deepest exudate occurs at the tips of certain folds, where the polynuclear leucocytes sometimes accumulate in masses and dissect off the epithelium. Numerous folds are wholly spared from exudate. It is not possible to give a reason for the variations shown. As a rule the epithelium is well preserved and shows many of its characteristic vacuoles. An occasional leucocyte is caught in emigration between the epithelial cells. Cells of the lymphocyte series are almost never in evidence. Between the folds there is considerable granular material with polynuclear and desquamated ependymal cells.

The floor of the fourth ventricle fails to show the pyogenic membrane suggested in the gross. The gross appearance was produced by an extensive local acute infiltration and formation of fibrin which permitted stripping off the superficial gray matter in a single mass. The fibrin collects particularly in the walls of small vessels, many of which are no longer pervious. The most prominent cells in the subependymal tissue are polynuclear leucocytes, some of which approach closely or seem to bury themselves in dying nerve cells. The neuroglia reaction does not go beyond swelling and process formation in the cell bodies.

At the edge of the abscess the intima of the arteries is raised by polynuclear leucocytes and may be stripped away. The large vessels remain pervious; it is probable that the smaller vessels become blocked at their origins. The abscess contains considerable fibrin. The polynuclear leucocytes far outnumber the mononuclear cells which are chiefly of the type with vesicular nuclei. The mononuclear cells in the free exudate are not very often phagocytic. The optic nerve shows edema and exudate of polynuclear leucocytes, together with a few phagocytic cells, in both the subarachnoid and subdural spaces.

CASE 6.—C. W., a male, aged 52, was admitted to the service of Dr. J. L. Ames at the Boston City Hospital, Jan. 21, 1904.

Clinical History.—Gonorrhea at twenty-seven. Rheumatism for ten years. Heavy drinker. Little alcohol for four days. The day before entrance fell while riding on car platform, procured one drink of whisky, lost consciousness and was brought to hospital. On admission dull, tremulous. Showed systolic murmur at apex transmitted to axilla and systolic whiff in arteries. Arteriosclerosis. Reflexes normal. Delirium with motor excitement set in but was replaced later with prostration. Slight nystagmus and deviation of eyes to right; pupils equal, reacting to light. Pulse rose to 160, respiration to 60, temperature to 105. Some spasticity of arms and legs. Râles appeared over both chests. Death, Sept. 26, 1904.

Autopsy Findings.—The autopsy, performed four hours after death by Drs. R. L. Thompson and N. H. Gifford showed:

Head: Hair black and fairly thick. Scalp normal. Calvarium thin. Dura adherent to calvarium. Sinuses contain cruor clot. Arachnoidal villi are fairly well marked. Meshes of pia contain over 50 c.c. cloudy, greenish-yellow, fairly thin fluid. Greenish and yellowish-white, fine and coarse thread-like markings along pial sulci. Both small and large vessels are moderately congested. Vessels of circle of Willis show slight diffuse thickening. Convolutions are well rounded and of fairly soft consistence with slightly congested vessels. Ventricles contain a few c.c. clear and pale yellow fluid. Cysts (1 to 3 mm. in diameter) stud choroid plexuses of both lateral ventricles. Pons and medulla of reduced consistence. Substance on section shows nothing remarkable.

Spinal cord: Fluid turbid. Pia thick and greenish-yellow. Cord soft.

Anatomic Diagnoses.—Acute leptomeningitis and encephalitis. Acute bronchitis. Edema and congestion of lungs. Chronic mitral endocarditis. General arteriosclerosis. Chronic splenitis. Chronic fibrous pleuritis. Chronic fibrous pericarditis. Chronic external pachymeningitis. Apical scar of left lung. Cysts of choroid plexus.

Microscopic Findings.—Cultures from heart's blood, lung and brain showed pure *Streptococcus pyogenes;* from liver, spleen and kidney, *Streptococcus pyogenes* and *B. coli.*

The cortical meninges are edematous and contain an exudate of polynuclear leucocytes which enclose numerous pairs of streptococci. Numerous chains of streptococci lie free in the granular material deposited in the pial meshes. Large phagocytic cells are rare. Single polynuclear leucocytes are found at rare intervals imbedded in the intima of the arteries; mononuclear cells are still rarer in this locus.

The severest lesion in this case affects the large sulcal veins, whose walls may be distended with polynuclear leucocytes outnumbering the original cells making up the wall. In the neighborhood of the injured veins there is an accumulation of large mononuclear cells; but these fail to be phagocytic in many cases, either for polynuclear leucocytes or for bacteria. Next to the severely injured veins, the larger arteries also exhibit the deepest infiltration of the intima with polynuclear leucocytes. The spinal meninges show an early exudate with few large phagocytes. Vascular lesions were not prominent in the blocks examined.

CASE 7.—L. H., a girl baby, born Dec. 25, 1904.

Clinical History.—Breast fed, had a cold at five weeks, but rapidly got well of it. The mother had sore throat, pain in back and legs, and fever when her child was about seven weeks old; the child at this time showed nothing but slight distension of the abdomen. A temperature of 104 appeared Feb. 23, 1905, throat and chest were negative. Admitted to Massachusetts Infants' Asylum with pulse 136, temperature 103, weight 5,000 gm. There was a slight red area on the left leg, attributed by the mother to a burn. The next day this red area had spread; the knee swelled; the head was held retracted. February 25, the whole left leg was swollen and tender but without increase of temperature, respiration shallow and grunting. The body temperature was maintained above 101. The leg improved; the morning of February 28, jaundice and convulsions appeared; general twitching, legs flexed, arms flexed across chest. The throat became filled with mucus. The chest showed râles, probably transmitted. March 1 the jaundice had increased, the head was held retracted, there was an occasional general twitching. The child vomited and failed to take food well. The eyes were fixed, the pupils dilated and sluggish. Death at midnight.

Autopsy Findings.—Examination 12 hours after death by Dr. E. E. Tyzzer showed: Murky limpid fluid beneath dura. Pial meshes contain murky bile-stained exudate. Exudate thick over cerebellum, thinner over cord. Murky bile-stained fluid exudate in ventricles.

Anatomic Diagnoses.—Acute cerebrospinal meningitis (*Stereptococcus*). Septicemia. Icterus (gall bladder and ducts normal).

Microscopic Findings.—Cultures showed *Streptococcus pyogenes* pure in heart's blood and liver, mixed with a *Staphylococcus* in spleen.

Cortex Cerebri: The meshes of the pia mater are distended with cells, of which the large mononuclear cells greatly outnumber the rest. The large mononuclear cells are phagocytic for numerous pairs and chains of streptococci. The inclusion of other exudative cells is frequent, but by no means so prominent as the bacterial phagocytosis. Large phagocytes of an omnivorous character are found, with vacuoles containing fat, mononuclear cells, polynuclear leucocytes and bacteria. Polynuclear leucocytes are frequent, but tend to show signs of degeneration. Cells which can be identified as belonging to the lymphocyte series are not frequent. A few cells of the plasma cell type, occasionally with two nuclei, lie in the adventitiæ of the vessels.

Cerebellum: The exudate varies in character, but shows everywhere a certain number of polynuclear leucocytes. Colonies and chains of streptococci abound in the superficial pia mater, and as a rule are enclosed within cells, both within polynuclear leucocytes and within large phagocytic cells. The bacteria seem to pass through an eosin staining stage before complete digestion. Except in the deepest places of the exudate opposite the mouths of the sulci, the polynuclear leucocytes are outnumbered by the large phagocytic cells. It is not infrequent to find cells phagocytic for polynuclear leucocytes which are themselves phagocytic for bacteria. In the sulci the connective tissues are packed with large vacuolated cells which accommodate themselves readily to changes of shape in the spaces they occupy. There are a few cells of the lymphocytic series, often with vesicular nuclei or with chromatin not murally arranged; but cells of the finished plasma cell type are rare.

Spinal Cord: The large phagocytes containing several kinds of cells and bacteria are prominent in the looser tissues. The adventitiæ of the vessels contain also a moderate number of cells of the lymphocyte series. The arteries show intima occasionally lifted by edema, with rarely an exudative cell beneath.

Case 8.—C. H., a hydrocephalic imbecile, aged 45, entered Dr. H. W. Mitchell's service at the Danvers Insane Hospital Oct. 13, 1905, and died Jan. 24, 1906.

Clinical History.—Dull at school. "Always ailing." Never could earn his living. Became vagrant several weeks before admission. Impairment of memory. Romberg sign absent. Gait fairly steady. Coarse tremor of fingers. Left pupil slightly irregular and without reaction. Knee jerks lively. Achilles reflexes brisk, with slight clonus. Plantars present. Spurious clonus of both ankles. Arm reflexes lively. Movements slow and listless. No spontaneous conversation. Memory poor. Limitation in range of thought. Lack of ideation.

Fainting spell two weeks before death. Decubitus. Pneumonic area in right lung. Death.

Autopsy.—Autopsy, performed by Dr. E. E. Southard, showed:

Head: Hair is gray and thin. Scalp strips readily. Calvarium thin, without diploë. Dura not adherent to calvarium. Dura distended. Sinuses contain liquid blood. Arachnoidal villi in moderate amount. Dura strips readily from pia except over ascending frontal gyri, where, particularly on the left side, the dura and pia are gummed together by a plastic stringy yellowish-gray exudate, covering an area on each side scarcely larger than a dollar and thinning out gradually at edges. There is no gross connection between this exudate and the otitis media of the right side. Except at the vertex, the pia mater is without exudate or edema and shows a few fibrous streaks over sulcal veins. The substance of the brain, cerebellum, interbrain, pons and bulb, exclusive of fluid contained in the ventricles, weighs 960 gm. The fluid withdrawn from the ventricles measures 1,300 c.c. The sulcation of the brain is rich but chiefly superficial and gives the impression of an alligator skin bag. The pia strips readily from the substance. Many of the sulci run inward for a few millimeters and bend at right angles, assuming a position concentric with the hemisphere surface for a few millimeters. It is not possible to homologize the sulci found with the sulci of the normal brain. The Sylvian fossa is the sole landmark on the flank of the hemisphere. Incision of the ventricles and withdrawal of the contained clear liquid show basal structures of a normal appearance, but almost total absence of callosal and fornix tissue. The walls of the ventricles are thinnest above and thickest below and behind. At the vertex the cortex and underlying white matter measure in places no more than 1.5 cm. The walls of the ventricles are of smooth and normal appearance. The cerebellum is of normal appearance and consistence. Lower structures are grossly normal. Right middle ear contains semi-liquid yellowish-green pus communicating with a cavity 1.5 cm. in diameter, in the mastoid process.

Anatomic Diagnoses.—Purulent otitis media dextra. Localized purulent leptomeningitis (vertex). Congenital internal hydrocephalus, with atrophy of corpus callosum and fornix and with microgyria and thinning of cortical substance. Absence of diploë. Slight aortic sclerosis. Apical scar of left lung. Edema and congestion of posterior parts of lungs. Cholelithiasis.

Microscopic Findings.—Culture from left middle ear shows *Streptococcus pyogenes.*

Cortex Cerebri: Phosphotungstic hematein section shows diffuse loose meshed neuroglia tissue with delicate isolated fibrils running in all directions. In the cell layers of the cortex the fibrils are curly, but run, as a rule, radially. Just below the pia, they begin to run tangentially and unite in a thin, dense mat. The deposit is thickest at the bottom of the sulcus, and there are sometimes projections of glia into the pial tissues in this situation, recalling the picture of *Randsklerose*. Some of the cells of the subpial region show two or three centrosome-like bodies in a light space in the cell body. The gliosis is remarkably even and delicate and is not markedly perivascular.

Cortex with Exudate (Frontal Region): Hemorrhage, with numerous polynuclear leucocytes and mononuclear cells in about equal proportions. Many of the mononuclear cells are phagocytic for polynuclear leucocytes.

The neuroglia cells beneath the pia have swollen bodies; some have two or three nuclei.

Cortex from Various Regions of Right Hemisphere (Nissl Stain): Superior frontal, ascending frontal, ascending parietal, paracentral, calcarine, limbic, gyrus rectus, show unusual cell pictures characterized by an unusual relative cell richness suggesting the pictures presented by the cortex of lower animals. The richest cell picture is derived from the calcarine area. Right Ammon's Horn (eosin methylene blue, phosphotungstic acid hematein) shows a thin superficial fibrillary gliosis with delicate even fibrils, and centrally a regular rich felt work of even delicate fibrils with some stouter ones.

Choroid Plexus: Numerous concentrically-layered bodies, Villi few. Vacuoles few.

Caudate Nucleus: Nerve cells as wide apart as usual. The ventricle wall shows flattened cells having basal corpuscles (phosphotungstic acid hematein) but, as a rule, no cilia. There are no elevations like those in more acute internal hydrocephalus.

Cerebellum: Centrum album gyrorum apt to be slender.

Cord: Nissl sections show an occasional eccentric nucleus in anterior horn cells at several levels. Phosphotungstic acid hematein demonstrates no excess of neuroglia.

The striking point exhibited by this case is the reaction of the neuroglia to the acute leptomeningitis. This reaction is a cellular gliosis resembling in every detail the cellular gliosis of the normal adult brain. Although the case showed very slight resistance to the streptococcus infection of the middle ear, yet the cells of the meninges showed phagocytic tendencies resembling those of the normal adult meninges, and, so far as demonstrable, the polynuclear leucocytic exudate was in the process of clearing up by the mononuclear cells.

CASE 9.—J. O., a woman, aged 40, entered Dr. F. R. Sims' service at the Danvers Insane Hospital April 4, and died April 9, 1906.

Clinical History.—Headache, violence, delusions of persecution, incoherence, four days before entrance. Nursing child thirteen months old. Herpes of lips, skin lesions probably due to chafing, constant listlessness. Lay on right side with head retracted and drawn to left and eyes turned up and to the left. Gait tottering, with feet held wide apart. General tremor. Knee-jerks apparent. Babinski reflex doubtful. Limbs held rigid. Pupils widely dilated. Resistive, distractable, disoriented. Fever 103. Signs of pneumonia in right lung set in three days after admission. Death.

Autopsy.—Autopsy, performed by Dr. E. E. Southard, showed:

Head: Hair dark. Scalp normal. Calvarium thick, with abundant diploë. Two emissary vein foramina in parietal bones. Dura lightly adherent to calvarium in bregmatic region. Dura tense, not markedly injected. Sinuses contain liquid or freshly clotted blood. Superficial cerebral veins deeply injected. Dura and pia inter-adherent in region of arachnoidal villi, through yellowish, very fibrinous pus. Fine superficial injection of vessels everywhere, but very little congestion of veins except at vertex. Pia externally smooth and only slightly moister than usual. The sulci and gyral surfaces are in a few regions filled with yellowish fibrinous pus: the upper two-thirds of both fissures of Rolando, the upper thirds of both ascending parietal gyri and, to a less extent, the upper thirds of both ascending frontal gyri, both superior parietal lobules, both fossæ of Sylvius. The circle of Willis is wholly concealed by fibrinous pus. The cisternæ of the base are filled with cloudy liquid. The middle two-thirds of the basilar artery is covered with fibrinous pus. The loci of origin of the fifth nerves are marked by masses of pus. The pia over culmen monticuli is swollen to a depth of .5 cm. with pus. The great horizontal fissure of cerebellum contains stringy yellowish pus.

Brain weight, 1,310 gm. Gyri a trifle flatter than normal. Substance everywhere equally reduced in consistence. The olives are no harder on palpation than the remainder of the medulla. Cerebellum softer relatively than cerebrum, softest in vermis which in places is almost diffluent. The line of Gennari in the cerebrum is hard to make out. There is no focal difference in consistence in the cerebrum, even in the areas of most marked suppuration.

Ventricles contain a normal or only triflingly increased amount of fluid which is cloudy. At the tip of each posterior cornu is a small mass of fibrinous pus. There is no pus in third or fourth ventricles.

Cord: On incision of the lumbar dura, considerable cloudy liquid flows out under slightly increased tension. Dura everywhere pinker than usual. Pia everywhere cloudy, but puffed out with yellowish fibrinous pus in cervical, middle thoracic, and lumbar regions notably behind. The root ganglia are frequently swollen.

Middle ears both free from pus. Cribriform plate apparently normal. Sphenoidal sinus filled with fibrinous pus. Nasal mucosa of right side swollen, injected, on left side apparently normal. Pituitary body soft, shows traces of pus on upper surface. Optic nerves, third nerves Gasserian ganglia (notably beneath), to a less extent seventh and eighth nerves, are surrounded by pus as they leave cerebral dura. Left retina excised; shows no injection.

Anatomic Diagnoses.—Acute cerebrospinal leptomeningitis. Serofibrinous exudate of vertex, Sylvian fossa, interpeduncular space, pons, vermis and horizontal fissure of cerebellum, pia of cord, origins of cranial and spinal nerves, Gasserian and spinal root ganglia. Acute purulent internal hydrocephalus and seropurulent exudate in cisternæ. General edema of brain and cord, particularly of vermis of cerebellum. Empyema of sphenoidal sinus. Edema of lungs. Bronchopneumonia of both lower lobes. Herpes labialis. Numerous minute hemorrhagic lesions of back and thighs. Acute splenitis. Acute and chronic nephritis. Slight aortic and mitral sclerosis. Extra cusp to pulmonary valve. Chronic adhesive pleuritis (bilateral).

Microscopic Findings.—Smear from sphenoidal sinus shows tremendous numbers of organisms, probably all streptococci. Smear from vertex shows great numbers of polynuclear leucocytes and mononuclear cells but no organisms. Smear from purulent fluid of basal cisternæ shows a very few pairs of small diplococci within leucocytes. The results of blood serum cultures confirmed the findings by smear.

Examination of the tissue in this case, showed a remarkable variety of pictures. Leptomeningitis, although fatal, was in the process of clearing up. This clearing-up was taking place from above downward. The pus at the vertex, about the longitudinal sinus and in pial meshes was sterile. The dominant cells were mononuclear. They contained numerous polynuclear leucocytes and fragments of nuclear material, besides considerable fat. No organisms could be found in these tissues. The picture thus resembled that in a healing leptomeningitis of meningococcal origin.

The pus at the base, on the contrary, contained a few pairs or short chains of an organism, which proved to be *Streptococcus pyogenes* in culture. The meshes of the pia at the base showed a higher proportion of polynuclear leucocytes than the pus at the vertex. Mononuclear phagocytosis was in process; but the healing must be regarded as in a far earlier phase than that of the vertex.

Traversing the bone at the base of the brain and examining the mucosæ of the sinus, a picture of acute inflammation is found. The polynuclear leucocytes here far outnumber the mononuclear cells and the tissues are filled with countless chains of streptococci. The general picture in this case anatomically resembles that in a meningococcus case of meningitis. The clearing up of the exudate takes place irregularly and from above downward.

GENERAL CLINICAL SUMMARY.

Seven patients were male, two female. Seven patients were over 30 years old; two of these over 50. One was nineteen, one an infant. Five cases showed otitis media.

	DURATION OF ACUTE SYMPTOMS.	DURATION OF CEREBRAL SYMPTOMS.
Case 1	4 weeks	24 days
Case 2	24 days	3 days
Case 3	4 weeks	4 weeks (8 days?)
Case 4	13 weeks	Brief
Case 5	Chronic middle ear (6 years), 24 days	24 days
Case 6	7 days	7 days
Case 7	7 days	7 days
Case 8	2 weeks	2 weeks
Case 9	10 days	10 days

As will be seen by comparison with the durations in a series of pneumococcus cases reported by Southard and Keene,[2] the durations in these streptococcus cases run a trifle greater than in the pneumococcus cases.

GENERAL ANATOMIC SUMMARY.

The brain lesions vary in character and distribution. The leptomeninges showed lesions in all cases. Cases 4 and 3 were exceptional. Case 4 showed distension of the pial meshes with a flocculent liquid exudate (which might readily simulate the so-called meningitis serosa). On the other hand, Case 3 showed an opaque tense pia mater of the vertex, with a thin web of organizing tissue at the base (simulating the appearance of a late meningococcal infection). The other seven cases all showed a more cellular exudate, variously described as thick, tenacious or fibrinous, and as opaque yellowish or greenish in color.

The distribution of the pial exudate is interesting. Except the hydrocephalic (Case 8), the base showed exudate in all cases, if we include the serous case (Case 4); if we include Case 4 as an exudative case, in all cases except Case 3 (organizing) and Case 5 (fulminant operative case). The cord is involved from the base, as a rule, the ventricles from the base or from abscesses of the substance adjacent to the ventricles.

The lesions of the brain substance are various. Flattening of the gyri stands in close relation with involvement and probably with actual distension of the ventricles. When flattening is absent, the substance is soft and moist and may be finely injected. No case of cortical flattening fails to show exudate in the ventricles; but in early stages of ventricular exudation the sulci may flare normally. Frank abscesses occurred in Case 2 (right temporal lobe) and Case 5 (right cerebellar hemisphere).

Cases 1, 2, 4, 5, 8 showed otitis media. Of these Cases 1, 2, 5 came to mastoid operation. Case 4 was an erysipelas case. The nasal sinuses were affected in Case 9. Of the others Cases 3, 6, 8, 9 showed lung lesions, which can not be certainly brought into relation with the leptomeningitis. Case 7 showed septicemia with icterus. Decubitus of one buttock occurred in Case 1, in multiple areas in Case 8, hemorrhagic cystitis in Case 2.

Of chronic lesions, whose relation to the infection can not be asserted, the following occurred: arteriosclerosis in Cases 1, 4, 9; chronic pleuritis in Cases 1, 2, 3, 4, 6; chronic internal hydrocephalus in Case 8.

GENERAL SUMMARY OF MICROSCOPIC FINDINGS.

As in previous work with cases of *Staphylococcus pyogenes aureus* and of pneumococcus brain infections, alterations were found in several of the tissues. The lesions of the streptococcus series present a close resemblance to those of the pneumococcus series. Characteristic for both organisms are the lesions of the vessels. The vascular lesions (described in more detail in the paper on pneumococcus infections) may serve to distinguish the pneumococcus-streptococcus cases, as Dr. Councilman has suggested, from meningococcus cases, It would be less easy to distinguish these vascular lesions from those in tuberculous leptomeningitis, in which the occurrence of local necrotic areas might need to be considered in making a diagnosis from the tissues. With a sufficiently long series of cases, it might be possible to mark out, from the vascular lesions alone, the course of the disease leptomeningitis.

Not merely the vessel lesions, but also the meningeal exudates serve in their variety to show how complex is the question of the natural history of leptomeningitis. As indicated in the two former papers,[1, 2] the occurrence of exudates with numerous mononuclear cells of the lymphocyte series is in itself not sufficient to differentiate any one type of leptomeningitis, such as the tuberculous, the syphilitic, the general paretic. Plasma cells are ubiquitous. The meninges exhibit exudates of a very variable character in many infections and toxic conditions. Perhaps it is not immediately necessary to ascribe the variations of exudate to different qualities of pathogenic agent. It will be desirable to work out first the time relations of a few organisms.

GENERAL SUMMARY AND REMARKS.

The foregoing cases of streptococcus brain infection are of interest in comparison with the cases of pneumococcus brain infection described last year. The main results may be stated in connection with those of the pneumococcus study.

As with the pneumococcus series, the questions of main interest are brought up by the varying extent and effect of lesions like (1) arteritis and phlebitis, (2) the cellular infiltration of the meninges with its variation in respect to phagocytosis and (3) the attendant cellular and, in certain cases, fibrillar gliosis.

Clinically viewed, the cases are of various duration and run a trifle longer than the pneumococcus cases. The relation of streptococcus meningitis to lung lesions is less suspicious than that of staphylococcus or pneumococcus brain infections to lung lesions. The part played by lung lesions in bringing about meningitis has probably been overestimated. The streptococcus cases seem to be more pronouncedly "cerebral" or "meningitic" from the very start of acute symptoms than are the pneumococcus and staphylococcus cases, which are a little more "primary."

Anatomically viewed, the streptococcus cases preserve their resemblance to the pneumococcus cases, even to the production in some cases of small abscesses. Particular attention may be called to the case simulating meningitis serosa (Case 4). It would be well to review the cases of this disease to be found in the literature and exclude those without bacteriologic examination.

Considered histologically, the streptococcus cases again resemble the pneumococcus cases. The same relations of bacteria to leucocytes, of leucocytes to cells of the macrophage type are shown in the two series. The intimal infiltration of the arteries and the intimal proliferation and exudative lesions of the veins run parallel in the two cases. The occurrence of early fibrillar gliosis (in the sense of the production of new fibrils by the swollen neuroglia cells) is important. The interpretation of early fibrillar gliosis is not easy, since it is necessary to exclude extraneous causes (old age, arteriosclerosis, chronic active lesions) for its occurrence.

An extensive series of guinea-pig inoculations, which need not be reported in detail, confirmed the main result, viz.: the parallelism in action of the two organisms, pneumococcus and streptococcus. Orbital inoculations simultaneously in numerous animals with histologic examination of animals killed on successive days were employed as in previous work. The inoculations of the strains used, as a rule, produced no clinical sign, despite the suppuration present. As in the human cases, each of the lesions found is apparently wholly curable taken by itself.

The reversible character (to use a phrase from books of logic) of the phenomena is shown in the strikingly various pictures presented by the exudate in Case 9 taken from the vertex downward.

Indeed, it is rare to find in streptococcal, as in other forms of acute leptomeningitis, any single lesion which is necessarily incurable. It is probable that in many cases the patients die of toxemia. This toxemia may vary with the extent of the exudate. The amount of exudate which we see at an autopsy may mislead us in our idea of the proportions of the toxemia, since wide reaches of the pia mater may be sterile, though other parts contain multiplying organisms. Differential studies of the exudate in several places are essential if we are to get a fair sample of the conditions. Such studies might readily assume clinical importance.

The early glioses found in several cases are of some importance both in general and clinically. These glioses will be best considered in connection with those in tuberculous meningitis in a subsequent paper.

LESIONS OF THE GRANULE LAYER OF THE HUMAN CEREBELLUM

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Reprinted from

The Journal of Medical Research, Volume XVI., No. 1

(New Series, Vol. XI., No. 1), pp. 99-116, March, 1907

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LESIONS OF THE GRANULE LAYER OF THE HUMAN CEREBELLUM.*

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The granule layer of the cerebellum is peculiar in construction. The layer is very rich in cells, surpassing most regions of the nervous system in the proportion of cells to the unit of space. Very noteworthy, in comparison with the general cell wealth, is the relative paucity in this locus of interstitial substance. Barring its vessels, the layer is, so to speak, almost purely nervous in structure. A further peculiarity of the granule layer is one shared by adjacent layers, viz., an almost uniform character throughout the cerebellum. The several cell types, the fibers, and the characteristic acidophile structures of Denissenko form altogether a most complex-looking apparatus; but the complexity is a uniform complexity throughout the organ.

The most striking feature of the granule layer is doubtless the relative wealth of cells therein. There are few fixed tissues, barring tissues concerned with continuous generation of cells, elsewhere in the body which present so many nuclei to the unit of space. In the central nervous system itself, there are few loci which approach the granule layer in relative nuclear richness, excepting some parts of the limbic lobe and the stellate cell layers of the cerebral (particularly the calcarine) cortex. There is no good evidence of multiplication in the nerve elements of the granule layer, at any rate after early life.

Despite this general cell-wealth, the granule layer is notably lacking in neuroglia tissue, that is to say, in cells producing neuroglia fibrils, under normal conditions. This fact was observed by Weigert in 1895. The methods of Mallory

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* Received for publication Jan. 25, 1907.

Read at the annual meeting of the American Association of Pathologists and Bacteriologists, Baltimore, May, 1906.

and of Benda go far to confirm the point. This lack of neuroglia tissue in the granule layer is the more surprising when contrasted with the presence of considerable fibrillar substance, as demonstrated by the above methods, in adjacent layers. Thus the underlying white matter and the overlying Purkinje cell belt are well supplied with neuroglia fibrils, while the molecular layer still finds space among the branches of the Purkinje cell dendrites for a number of fibrils, even under normal conditions. The granule layer of the cerebellum may be logically grouped, therefore, with various peripheral nerve structures in the vertebrates, in its lack of neuroglia. This lack, however, is readily supplied under abnormal conditions.

Besides the relative cell wealth and (perhaps also relative) paucity of neuroglia tissue, the granule layer also shows a strikingly constant arrangement of the constituent elements, which holds not only throughout a given lamina but also, so far as known, throughout the cerebellar cortex. The cell arrangements, not merely of the granule layer, but also of the exterior layers, in the cerebellum are far more nearly uniform (or less differentiated ?) then the cell arrangements of the cerebral cortex. There is good ground for calling the cerebral cortex a composite of organs. So far, however, the cerebellum seems as uniform as it is complex. This fact has given rise from early days to the idea that the cerebellum acts as a unit. In any case, the granule layer is obviously a structural unit in the cerebellum.

What part shall be assigned to the granule layer in cerebellar activity? We might argue something of its functions from its situation between the core of white matter and the Purkinje cell belt. The presence of incoming and outgoing nerve fibers in the core of white matter obviously suggests that the activities of the cerebellar cortex complete an arc of impulses which flow in those fibers. It seems well established that the Purkinje cells are the locus of immediate origin for outgoing impulses. In case this is so, then the granule layer may probably serve, as seems likely from its site, as part of the centripetal mechanism.

As an example of the difficulties lodging herein, the hypothetical account of Kölliker, based on the work of Ramón y Cajal and others, may be cited. Kölliker (1896) regarded the Purkinje cells as the centrifugal elements, the moss fibers and climbing fibers (of the Golgi pictures) as the centripetal elements of the cerebellar cortex. Counting the Purkinje cells as the only centrifugal cells, it becomes hard to interrelate the remainder of the cells, classified by Kölliker as large and small granule cells, basket cells, and small cortical cells, which must all be related with the centripetal apparatus. Kölliker proposes that the moss fibers shall come into relation with the small and large granule cells, that the large granule cells shall be association cells, and that the small granule cells shall by means of their processes in the molecular layer come into relation with the Purkinje cell dendrites. This account leaves outstanding the basket cells and the small nerve cells of the cortex. Kölliker proposes that the climbing fibers and other centripetal fibers shall come into relation with these latter cells and these in turn with the Purkinje cell dendrites once more.

This account of Kölliker's yields some notion of the number of elements with which we deal. The account leaves out, moreover, the acidophile structures of Denissenko, which, as shown below, are remarkably resistant in disease.

Not to consider minutiæ at this point, it is evident that a true solution of these and kindred problems might be attained if we could differentially destroy the various elements in turn and watch the effect upon the activities of the apparatus in lower animals. A slower but perhaps surer method of attack might be to watch the effect of such differential or uncomplicated destruction of the various elements in man in the course of disease.

In default of a more rapid method of work, I have thought it profitable to look through a considerable number of cases, both with and without gross signs of cerebellar disease, to find what are the common lesions of the granule layer. An ulterior object was to arrange the elements of the granule layer in a series according to their resistance to injurious agents.

The present work is related to some previous work printed in 1905, where I described in some detail the characteristic lesions of the exterior layers in cases of marginal sclerosis in the human cerebellum. To these lesions there proved to be a rather obvious natural history. Thus the early lesions found in leptomeningitis (particularly tuberculous) could be aligned with the later lesions in local ischemia (well shown in infarctions of luetic origin). The series of changes thus made clear were used to explain the peculiar appearances — fibrillar overgrowth in three planes — in cases of stationary or terminal fibrillar gliosis. The first stage of this fibrillar gliosis in three planes was shown to be an overgrowth of the characteristic radial fibrils (Bergmann's fibers) of the molecular layer, an overgrowth frequently related with the death of Purkinje cells. The cells of origin for these radially shooting fibrils were found to be certain neuroglia cells in the Purkinje cell belt. In accord with the established conception of the Purkinje cells as the cells of least resistance in the cerebellum, it was found that the Purkinje cell belt is the locus of earliest activity in repair.

At present I wish to consider in a similar way the natural order of lesions in the inner (granule) layer of the human cerebellum. I have presented the cases on which the points are based in summary form. I have used various special methods on the material, but have depended for the general analysis of the findings in the granule layer upon various methods after fixation in Zenker's fluid, especially upon eosin and methylene blue, Mallory's aniline blue, and Mallory's phosphotungstic acid hematein methods, used on paraffine sections.

Case I. Case of defective girl, born without the use of instruments in the eighth month, one of twins (the other still-born). Slight evidence of consciousness or orientation (even for mother). General rigidity. Food given with difficulty. Constipation. Lived in cradle on its back. Convulsive seizures began after twentieth month. Death in thirty-seventh month from bronchopneumonia.*

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* For clinical history in full, see Bullard and Southard. A case of idiocy in a child with cystic hemispheres. Medical and Surgical Reports, Boston City Hospital, XV., 1905.

The autopsy showed gross cerebral changes. The ground plan of the cerebrum was preserved, but the substance of each hemisphere was largely replaced by a closed cystic cavity, independent of the ventricles. The interiors of the cystic cavities were traversed by delicate strands of neuroglia tissue. The pyramidal tracts had failed to develop.*

The cerebellum showed no reduction in size and possessed the usual markings.

The microscopic examination of the cerebellum in this case showed that the granule layer was far richer in cells, relatively to the unit of space, than the granule layer of the adult (see Plate IV., Figs. 1 and 2). The small cells called granule cells possess somewhat more vesicular nuclei than similar cells in the adult and are more closely packed together. The clear spaces between granule cell groups are more sharply marked off than in the adult and contain in some cases the characteristic acidophile structures of Denissenko. In other cases, however, the clear interspaces contain a nucleated structure in place of the non-nucleated structure of Denissenko. These structures, not seen in the adult, are spread not alone through the granule layer but also through the core of white fibers (where also they fail to occur in the adult). These cells have large homogeneous cell-bodies, rounded or oval in shape, and vary in size to above 60μ. They are supplied with single or sometimes with two rather dense central nuclei (see Plate IV., Fig. 3). There is no evidence from the tissues of this case that these cells produce neuroglia fibrils. It is still probable that they are cells of the interstitial or neuroglia series. It is not improbable that these cells in the granule layer may give rise to the acidophile structures of Denissenko. Of this, there is no proof, save that of suggestive situation and certain apparent transitions.

The case brings out the relatively even greater cell-wealth of the granule layer early in development and the occurrence or persistence of certain cells, probably neuroglia cells, which may be related with the development of the acidophile structures of Denissenko. The cell arrangements throughout the cerebellar cortex are uniform.

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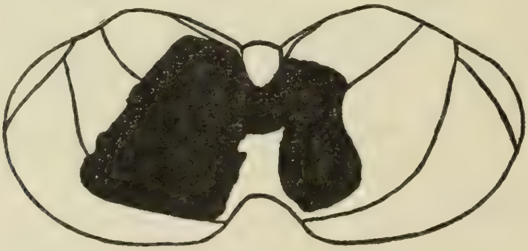
* For photographs showing cerebral aplasia of this case, see Bullard and Southard. Cystic aplasia of the cerebral hemispheres in an idiot child. Journ. Med. Research, XIV., 2, January, 1905.

Case II. Epileptic imbecile of sixty-five years. One brother imbecile. Learned to walk at four or five. Never learned to speak beyond "yes" and "no," "papa" and "mamma," with a few oaths. Could make his wants known to family. Earned living by work on farm till fifty. Grew more childish and irritable later in life. Confused spells with hands raised to head at various times throughout life. Epileptic convulsions the last seven years of life. Occasionally noisy and homicidal. On admission, slight swaying in Romberg position. Knee-jerks dull, but equal. Other deep reflexes diminished. Superficial reflexes not obtained. Pupils small, oval perpendicularly, reacted within narrow limits. Petit mal and occasional severe epileptic convulsions during hospital stay (eight months). Death nine days after taking to bed with increased stupidity and signs of pneumonia in lower back.*

The autopsy † showed death due to typhoid fever and lobar pneumonia. The trunk showed little else abnormal, save half-sized testes, one containing a small cyst. There was coronary arteriosclerosis of moderate grade. The skull was symmetrical, the diploë congested. The pia mater was everywhere clear. The cerebrum showed anomalous fissuration, symmetrical in the anterior portions, both lateral and mesial, of both hemispheres. The affected lobes showed not only a microgyria with obscuring of normal markings, but also multiple fine corrugations of each gyrus with the thin pia mater exactly lining each irregularity.



The cerebellum showed an absence of lamination in a broad area over the upper surface (see text-figure). The parts without laminæ were the following: Anterior half of culmen monticuli, inner two-thirds of left lobus culminis, inner two-thirds of left lobus clivi, a narrow strip in the left lobus cacuminis posterior to the postclival fissure, inner third of right lobus culminus, inner third of right lobus clivi (with preservation of laminæ for a narrow strip anterior to postclival fissure). The clivus and the substance adjacent to the posterior cerebellar notch showed normal lamination.

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* Clinical notes through kindness of Dr. C. B. Sullivan, assistant physician to the Danvers Insane Hospital.

† Autopsy notes and cerebellum through kindness of Prof. A. M. Barrett of Ann Arbor, Mich., during whose service as pathologist to the Danvers Insane Hospital the case came to autopsy.

The microscopic examination of the non-laminated region of the cerebellum in this case showed interesting translocations of various structures. Isolated cells and groups of cells of the Purkinje cell type exhibit how little necessary relation exists between the development of Purkinje cells and that of the granule layer. Purkinje cells occasionally abut upon stray fascicles of white matter, as demonstrated in Weigert myelin sheath preparations.

The cell groups representing the granule layer are, as a rule, rounded like the normal granule layer, but occur in rather slender, anastomotic or isolated masses, as a rule, bordered by Purkinje cells (see Plate V., Fig. 4). There are occasional complete rings of cells, grouped to imitate the normal granule cells with cells of the Purkinje cell type both inside and outside the ring (see Plate V., Fig. 5). The cell-richness of these abnormal granule-cell accumulations is within normal limits. The acidophile structures of Denissenko are occasionally seen.

The molecular layer seems to be more irregular in development than the other layers and is subject to more sudden changes of contour. A layer roughly resembling the molecular layer invests the flat surface of the region affected and in some cases abuts directly upon fan-shaped masses of medullated fibers.

The case brings out the possible independence of development of the granule layer and the Purkinje cell belt (see Plate V., Fig. 6). In a case of severe early developmental injury, the general cell relations (possibly the general effectiveness of the apparatus) can be altered, yet the granule layer preserves independence as if it were to some degree a tissue unit.

Case III. C. K., salesman of forty-seven years, entered Dr. G. B. Shattuck's medical service at the Boston City Hospital Dec. 22, 1902. Alcoholic, obese. At thirty-seven in bed four to five weeks with rheumatic fever, at forty-one in bed four weeks with scarlet fever, at forty-three in bed eight weeks with broken leg.

Patient took to bed five days before entrance with weakness and anorexia.

On entrance apathetic, râles in lower right back, abdomen tympanitic, distended, Babinski reflex on both sides, leucocytes 20,000. Delirium next day, at first restless, later more quiet. Rose spots December 26th. December 28th difficult to rouse, quiet, numerous rose spots, fever, respiration rapid and difficult, leucocytes 8,800. Widal reaction absent. The râles increased, respiration became difficult, mucus could not be coughed up, cyanosis developed. Death eighth day after entrance, thirteenth day after symptoms developed.

The autopsy showed: Brain wt. 1,190 grams. Dura quite adherent to calvarium. Numerous pacchionian granulations along longitudinal sinus. Pia injected. Large amount of subpial fluid. Cortex soft and edematous. White matter normal. Lateral ventricles contain more fluid than normal. Lower portion of right hemisphere of cerebellum contains six or eight minute homorrhages, two of them extending into dentate nucleus.

Diagnoses. — Typhoid fever; acute splenitis; lymphnoditis (ileocecal group); acute bronchitis; early pneumonia; edema of cortex; suppurative otitis media; chronic interstitial orchitis.

The microscopic examination of the cerebellum in this case showed small hemorrhages into the molecular layer derived from small pial vessels, as a rule at the base of sulci. The molecular layer itself showed little reaction beyond slightly more vesicular nuclei in the neuroglia cells and pyknotic nerve-cell nuclei.

The reaction in the interior layers beyond the zone of destruction is striking see Plate VI., Figs. 7 and 8). For here, whether through pressure or poison, there is evidence of differential cell-destruction. Whereas the lamina as a whole is quite normal in cell supply, the region opposite the effusion of blood shows death of Purkinje cells and a sharply marked zone of granule cells with pyknotic nuclei. The acidophile structures of Denissenko are, however, not visibly altered.

The case is in effect a natural experiment to show that differential destruction of cellular elements occurs in the cerebellum and to give an idea of the order of cell destruction.

CASE IV. A poorly developed and ill-nourished male of twenty-five years. Never a bright scholar, mill worker. Albuminuria and defective memory three years before commitment, six years before death. Exaggerated knee-jerks, slow hesitant movements, complete disorientation, imperfect insight into condition, diminished effect. Hallucinations elicited two years after commitment. Death with unchanged signs.*

The microscopic examination of the cerebellum in this case showed the granule layer in numerous laminæ infiltrated with deposits of hyaline and lime salts (see Plate VII., Fig. 9). The granule cells are locally thinned out. The granule cells which remain are well preserved. There is a considerable supply of fibrillar neuroglia tissue throughout the laminæ both near the lime deposits and remote from any. Similar small lime deposits lie in the white matter near the granule layer. The acidophile structures of Denissenko are preserved.

CASE V. A. A., theater-employee of thirty-two, entered Dr. J. W. Bartol's service at the Boston City Hospital Aug. 25, 1905. The patient had been subject to diphtheria and scarlet fever in youth, besides "bilious" attacks followed by jaundice and vomiting. Gonorrhea. Syphilis denied. At twenty-eight the patient had an attack of headache, vertigo, nausea, and vomiting, lasting at least a fortnight. Two attacks afterward. All three were regarded as due to nephritis.

Four weeks before entrance (five weeks before death) occipital headache, vertigo, anorexia, pain in back, palpitation and dyspnea on exertion, cramps in feet at night, and increased amount of urine appeared. Gave up work eight days before entrance. Vomiting all one day four days before entrance.

On entrance, uremic odor to breath, systolic murmur in mitral region, marked arteriosclerosis, knee-jerks present and equal, spurious ankle-clonus. Convulsion lasting fifteen minutes the day following entrance. Swelling of eyelids. Twitching of head and arms. A swelling size of fist on right side of neck developed September 2. The patient became worse in the evening and died an hour later having developed considerable rigidity of neck, Kernig's sign, increase of knee-jerks, bilateral ankle-clonus.

The examination of the head † showed normal scalp, calvarium, and dura, well marked arachnoidal villi and basal vessels without gross sclerosis. Considerable subpial edema. Brain weight 1,435 grams. Substance uncommonly firm. Small cysts of choroid plexus. Pons, medulla, mid-brain, basal ganglia negative on section. Cerebellum showed nothing abnormal on section.

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* Clinical notes through the kindness of Dr. H. W. Mitchell, senior assistant physician to the Danvers Insane Hospital.

† I am obliged to Dr. C. W. Duval, pathologist to the Montreal General Hospital, for the tissues of this case, examined by him while assistant in pathology in the Boston City Hospital.

The aorta showed sclerosis without calcification. There were small old foci of calcification in the liver, and small calcareous masses in the pyramids of the kidneys. Chronic diffuse nephritis. Chronic splenitis. Death was due to acute purulent pericarditis.

The microscopic examination of the cerebellum in this case showed lesions similar to those of Case IV., but of severer character (see Plate VIII., Figs. 10 and 11). The acidophile structures remain intact. Numerous active fibril-producing astrocytes are found in the granule layer. The fibrils often embrace the acidophile structures closely, but apparently fail to pierce them (see Plate VIII., Fig. 11).

Case VI. Undersized negro, of twenty-three years. Hutchinsonian teeth. Backward at school, of limited mental capacity. Tendency to fall down at play. Change for the worse asserted during last five or six years of life. Sold newspapers or blacked shoes up to within a year of death. In last months of life, showed general incoördination (coarse drunken movements) and tremors, with shifting gaze and tendency to nystagmus. Disorientation for time, place, and persons, confusion with coarsely relevant replies to questions, ill-defined and transitory delusions of persecution, auditory, visual, and tactile hallucinations, defective memory. A few remissions with slight clearing up of confusion.

The autopsy showed death due to an early bronchopneumonia (numerous staphylococci). The organs of the trunk were small and firm (heart, 130 grams; spleen, 25 grams; liver, 640 grams; kidneys together, 150 grams), and suggested, as did the brain, a hypoplasia. There was persistent thymus tissue in a tongued shaped mass, measuring 3×2×0.5 centimeters above the aortic arch. The femoral marrow was red and jelly-like, suggesting red bar-le-duc. The arch of the aorta showed a few plaques of sclerosis. The brain weighed 965 grams and showed chronic diffuse and focal leptomeningitis roughly corresponding with a diffuse cerebral and cerebellar gliosis. The cerebrum also showed focal sclerotic nodules, resembling those described in idiots by Bourneville, in the temporal gyri. Occipital microgyria. Gliotic lesions with pigmentation in posterior horns of spinal cord, perhaps related with a hydromyelia demonstrable at some levels.

The cerebellum was as firm as the normal olivary bodies. The hemispheres were symmetrical and of a normal appearance, save that the laminæ were slightly narrower than usual and very compactly set. The pia mater showed a diffuse haziness, best marked over the superior surface, besides focal thickenings of an unusual character, linear mounds of fibrous tissue running at an angle to the laminæ. There was no notable overgrowth of fibrous tissue at the base.

The microscopical examination showed in the cerebellar cortex the greatest possible gliosis consistent with maintenance of normal topography.

The meninges show an infiltration of moderate degree with cells of the lymphocyte series and pigment-bearing cells, together with edema over the most contracted lamellæ.

The vessels of the central white matter near the origins of the laminæ often show collections of granular material (possibly lime salts) ensheathing the intima. This process is less common in the meninges.

Some of the lamellæ have preserved a good number of Purkinje cells. Numerous marginal lamellæ show no Purkinje cells. Occasional Purkinje cells show two or more nuclei.

The molecular layer shows everywhere a notable increase in Bergmann's fibers, and in many lamellæ is diminished one-third or more in depth. A number of marginal lamellæ show a deep superficial zone of concentric fibrils in the locus of the fetal cell layer; this new layer is unevenly developed and recalls the (somewhat more richly cellular) focal superficial gliosis of the temporal cortex cerebri of the same case.

The granule layer shows a diffuse aplasia, and a thinning out of the granule cells, especially well shown toward the extremities of the lamellæ. The granule cells preserve in many places their usual grouping, but the picture gradually changes to one of granule cells of focal occurrence only or to one of complete loss of granule cells. The degree of fibrillary gliosis seems to parallel the loss of granule cells.

The white center shows a less dense gliosis (replacement gliosis) not in particular relation to vessels with occasional cystic deficiency near tips of laminæ.

Cerebellar cortex (myelin sheath stain). — In some cases almost total absence of fibers in centrum album gyrorum, in many cases pronounced thinning out toward the tip. A few fibers are almost everywhere preserved in the molecular layer. (Marchi) — Black granules, larger and less even in distribution in the centrum album than in the cerebral cortex by the same method.

Dentate nucleus. — High neuroglia fibril content about large nerve cells and notably within the nucleus (see especially phosphotungstic acid hematein preparations). The Marchi preparation shows large scattered drops particularly within nuclear limits.

I have been able to collect a few notes from the literature concerning the granule layer of the cerebellum in disease.

Bergmann,[1] 1861, described findings in an atrophic cerebellum, which, as Weigert has pointed out, are in part erroneous, since Bergmann regarded the radial fibers which now bear his name as forming a reticulum. Bergmann also described a paling-out of the granule layer and a diminution in number of granule cells.

Obersteiner,[2] 1871, described a focal lesion in the right cerebellar hemisphere in a man of thirty years dying of acute yellow atrophy of the liver. Obersteiner there called attention to the absence of Purkinje cells, to the development of numerous radial fibers in the molecular layer, and to a layer of concentric fibers (which he terms Ependymschicht) in the inner portion of the molecular layer. The Purkinje cell layer is figured as full of gaps and without cell accumulation. Obersteiner compares the granule layer to lymphoid tissue, remarking that the granule cells are held in a sponge-like ground substance. He found, also, in the granule layer a few larger elements which he regarded as degenerate nerve elements (one possessing two nuclei).

Kirchhoff,[3] 1882, described two cases of atrophy and sclerosis of the cerebellum, in a girl of seven (symptoms beginning at five years) and in an imbecile woman of twenty. Kirchhoff compared the appearance of the atrophic area in the superior vermis and left cerebellar hemisphere in the girl to the appearance of the embryonic cerebellum at the sixth month. Kirchhoff compared the condition of the more extensive cerebellar atrophy in the imbecile with the appearance of the embryonic cerebellum at the seventh month. In both cases Purkinje cells were absent from the atrophic areas. From the even diameters of the granule layer throughout the sclerotic laminæ in the imbecile, Kirchhoff argues the embryonic date and origin of the lesion It is doubtful whether this argument can be upheld.

Sommer,[4] 1884, described cerebellar atrophy and sclerosis in a hydrocephalic of thirty years. He found the granule layer reduced from 300 to about 60μ in depth. The granule cells seemed normal but reduced in number and wide apart. In the area normally occupied by granule cells, Sommer found a granular ground substance in which are irregularly scattered many rounded nuclei. The small vessels had thickened walls. Sommer regarded these changes and those in the white matter as secondary to the absence of Purkinje cells and other alterations in the gray substance.

A. Meyer[5] (Osnabrück), 1890, figured diminution of nerve fibers in the cerebellar cortex, chiefly in cases of general paralysis, by means of Weigert's myelin sheath method. With respect to the other elements Meyer says that carmine preparations demonstrated no other alterations in the outer or in the granule layers, and believes that there is no alteration or numerical reduction in the Purkinje cells. He regarded the degeneration as primary and analogous to similar alterations in the cerebral cortex.

Weigert,[6] 1895, found "*so gut wie gar keine*" neuroglia fibers in the granule layer under normal conditions, and this in contrast with the Bergmann fibers of the molecular layer, the fibers surrounding the Purkinje cells, and the normally rich supply of fibers in the white matter. Weigert, however, mentions the increase of fibers in the granule layer in general paralysis and other conditions.

Raecke,[7] 1901, described an examination of the cerebellum in fifteen subjects of general paralysis by Weigert's neuroglia method. Raecke confirmed Weigert's observation of an increase of Bergmann's fibers in the molecular layer. Raecke found a peripheral zone of gliosis and a gliosis about the Purkinje cells. It is curious that the Purkinje cells, according to Raecke, show little or no change except in the severest foci, and Raecke is apparently of the opinion that the Purkinje cell alterations are secondary to the gliosis. The process in the granule layer was studied in the severest foci. Here the lost granule cells are simply replaced with neuroglia. Raecke goes on to say that — "since with every overgrowth of supportive tissue, whether primary or secondary, there must correspond a certain loss of nerve elements," it is probable that the earliest change in general paralysis affects the dendrites of the Purkinje cells.

INTERPRETATION OF FINDINGS. — The cerebellum is a good field for the study of differential lesions. There is a striking variety of structures in it. Yet this structural variety is, roughly speaking, the same throughout. The obvious structural unit is the cerebellar lamina. Each lamina presents a white core containing ingoing and outgoing fibers. Surrounding the white core is the gray matter of the cerebellar cortex. The elements of the cerebellar cortex comprise, (1) an important centrifugal apparatus — the Purkinje cells; and (2) a number of structures regarded as centripetal — the various structures of the granule layer, together with sundry elements of the molecular layer. The granule layer lies next to the white core and contains elements concerned presumably with the reception of impulses entering the lamina by way of the white core. The granule layer apparatus comes into relation with the manifold processes of the Purkinje cells which project into the molecular layer, in a fashion which is not obvious. The data of the Golgi impregnations here step in to demonstrate processes from the granule cells running outward to fall into relation with the dendrite forest of the molecular layer.

The course of a single impulse (an artificial abstraction in the cerebellum probably) might then be inward in a fiber of the white core to a granule cell, thence in a process to some dendrite of a Purkinje cell lying in the molecular layer, thence doubling on itself and running outward through the Purkinje cell and its single axis-cylinder to the white core again. It is of course doubtful whether any single impulse ever runs this uncomplicated course in the cerebellum. Not only have certain interposed elements been omitted in the series mentioned, but also it is highly probable that no single impulse goes far into the cerebellar cortex without starting up fresh impulses in several directions. The granule cell groups are precisely fitted for this, since little or no non-nervous material of the neuroglia type is discernible between the granule cells. Elsewhere in the cerebellum there are much more pronounced intervals between the nervous elements as well as a considerable supply of neuroglia which provides more effective surfaces of separation than the closely compact granule layer possesses.

Once running along Purkinje cell dendrites, it is difficult to see how a nerve impulse could be interrupted in its centrifugal course, although its intensity might conceivably depend upon the number of dendrites activated. If this conception be accurate, most of the transferent and inhibitory functions must be attributed to apparatus previously mentioned, namely, to apparatus centering in the granule layer.

Next to the granule cells the most prominent elements of the granule layer are the apparently homogeneous eosin staining structures of Denissenko. These are buffer elements imbedded in the anastomotic granule cell masses. Their functions may be to heighten, to depress, or otherwise to modify impulses which reach the granule layer. They may or may not alter in condition from moment to moment. It is possible, if improbable, that these eosin structures have no nervous function.

I have been studying the cerebellum, not so much in the hope of directly unfolding its functions, as to show what are the relative resistances of its elements to disease. In a previous paper I have described once more the familiar fact that the great elements of the Purkinje cell belt are the first to undergo destruction. I have also pointed out that in many types of lesion the Purkinje cell belt is the initial scene of activity, which activity takes the form of neuroglia cell overgrowth. When a lesion proceeds no farther than destruction of Purkinje cells, it is evident that the consequent alteration of function must be relatively coarse, tantamount perhaps to a mere suspension of functional discharge from the injured focus.

I have therefore looked over a number of cases to find examples of more exquisite injury to the centripetal or central apparatus, the apparatus which must have much to do with the coördination and perhaps with the inhibition of impulses. I have here presented a few cases to illustrate points of this nature. The most interesting result of this study is the observation that the eosin-staining structures of Denissenko are remarkably stable structures in comparison with the other elements of the granule layer.

The discovery of nucleated structures in place of the non-nucleated structures of Denissenko in a case of maldevelopment (Case I.) seems to offer hope that the development of these structures may be worked out. It is possible that the eosin structures of Denissenko stand in the same relation to nucleated structures in early life in which red blood globules stand to blasts. Work on this line is in progress.

The observation that Purkinje cells can develop independently of granule cells, and vice versa (Case II.), seems to be consistent with the conception of their functional independence outlined above. Granule cells appear to develop together and are supplied with the eosin structures of Denissenko.

A case of typhoid fever with small hemorrhages in the cerebellar pia mater (Case III.) offered a natural experiment in which both the maximum lability of the Purkinje cells and the initial neuroglia activity of the Purkinje cell belt are again demonstrated. The case likewise presented in the same region of focal atrophy necrosis of granule cells, among which however the eosin-staining structures of Denissenko persist.

Two further cases (Cases IV. and V.) demonstrated a curious deposition of hyaline material and lime salts confined largely to the granule layer. The lesion, of interest in itself, is here used to demonstrate the point that the eosin-staining structures persist despite the atrophy and death of numerous granule cells. In one case a delicate neuroglia overgrowth occurred, and the neuroglia fibrils are found embracing but not piercing the eosin-staining structures.

Work is in progress in the direction suggested by Case IV. Such a case demonstrates the possibility that, despite normal afferent nerves and a normal discharging apparatus (the Purkinje cells), there may be disorder of the most exquisite character in the central receptive apparatus (granule layer) of the cerebellum.

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DESCRIPTION OF PLATES.

PLATE IV.

FIGS. 1, 2, 3. — Cerebellum in Case I. (case of cystic aplasia of the cerebral hemispheres with absence of pyramidal tracts).

FIG 1. — Note the relative cell-richness of the granule layer. Compare with the normal cell supply of the granule layer as shown in Fig. 8.

FIG. 2. — Same case as Fig. 1. Granule layer showing supernormal cell-richness as compared with the adult. Note spaces between the granule cell clusters. Spaces contain single central nuclei.

FIG. 3 — Same case as Figs. 1 and 2. Large cells of white matter, one containing two nuclei and dark-staining central bodies. These cells are probably of the neuroglia series and possibly of the same type as those filling the clear spaces of the granule layer shown in Fig. 1 and particularly in Fig. 2.

PLATE V.

FIGS. 4, 5, 6. — Cerebellum in Case II. (Case of cerebellar anomaly: absence of lamination in part of superior surface of cerebellum in an epileptic imbecile).

FIG. 4 — Note irregular contours of tissue representing the granule layer. Heterotopia of Purkinje cells.

FIG. 5. — Heterotopia. Granule layer ring with Purkinje cells both inside and outside.

FIG. 6. — Group of Purkinje cells growing independently of the granule layer.

PLATE VI.

FIGS. 7, 8. — Cerebellum in Case III. (case of typhoid fever with small hemorrhages in the pia mater of the cerebellum). The two photographs are from the same lamina. Fig. 7 is taken from the injured side of the lamina, Fig. 8 from the uninjured side. The differences are due to the presence of a focus of pial hemorrhage opposite Fig. 7, absent opposite Fig. 8. The hemorrhage is not shown in Fig. 8, which exhibits its effects across the intervening molecular layer. Fig. 8 shows

1. Persistence of but one Purkinje cell, which was intensely eosinophilic and shows an eccentric nucleus;
2. Sparse and pyknotic granule cell nuclei in one focus adjacent to the Purkinje cell belt; and
3. Numerical increase of neuroglia cells in the Purkinje cell belt itself.

The lesions of Fig. 7 are shown nowhere else in the affected lamina or in adjacent laminæ. Fig. 8 shows essentially normal appearances.

PLATE VII.

FIG. 9. — Cerebellum in Case IV. (case regarded as dementia praecox). Lamina with coarse masses of lime, locally replacing groups of elements in the granule layer. Besides the large masses numerous smaller masses occur throughout the granule layer, and there is a diffuse delicate fibrillar gliosis throughout.

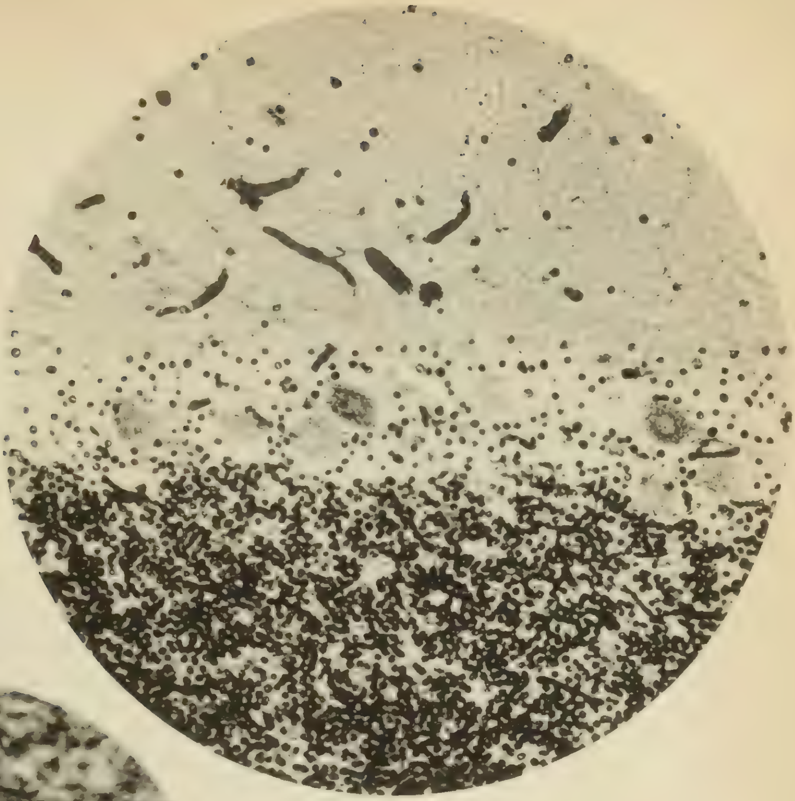
Plate VIII.

Figs. 10, 11. — Cerebellum in Case V. (case without nervous symptoms dying of acute purulent pericarditis. Foci of calcification found also in liver and kidneys). Compare Fig. 9. Marked atrophy of elements of granule layer. The granule cells preserve their arrangement in clusters. Small homogeneous apparently structureless bodies, slightly larger than granule cells, of a rounded or oval shape in section — structures (so-called "cells") of Denissenko — persist. Fig. 11 shows a swollen fibril-producing neuroglia cell. The fibrils stretch out to embrace a persistent structure of Denissenko.

Plate IX.

Figs. 12, 13. — Atrophy of granule cells with volume of layer largely maintained. Structures of Denissenko persist.

The Journal of Medical Research, Vol. XVI., No. 1, March, 1907.



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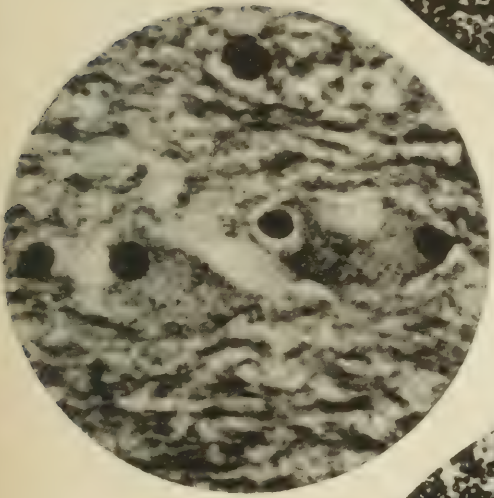

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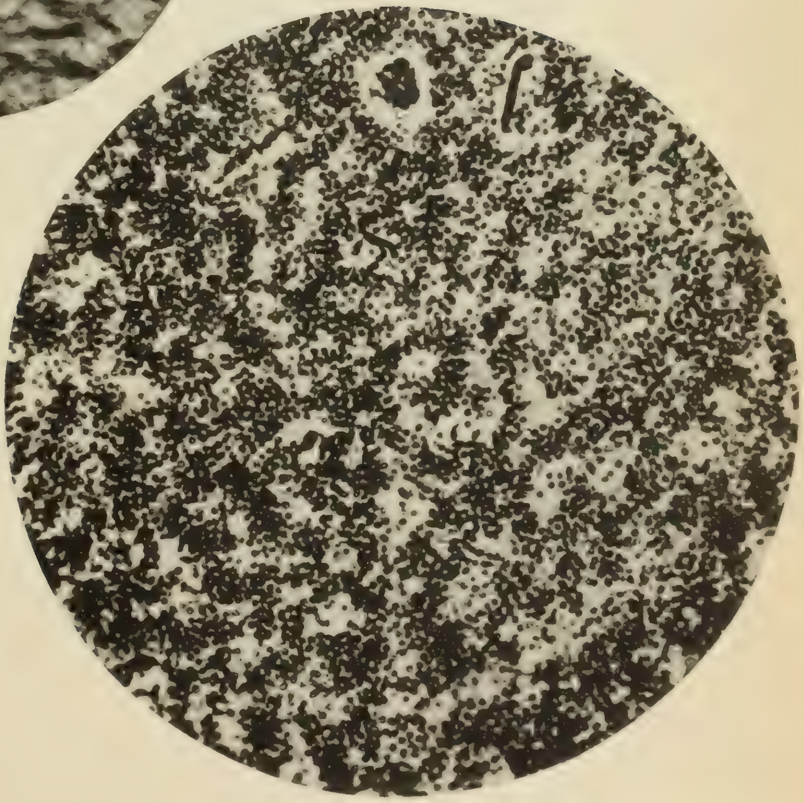

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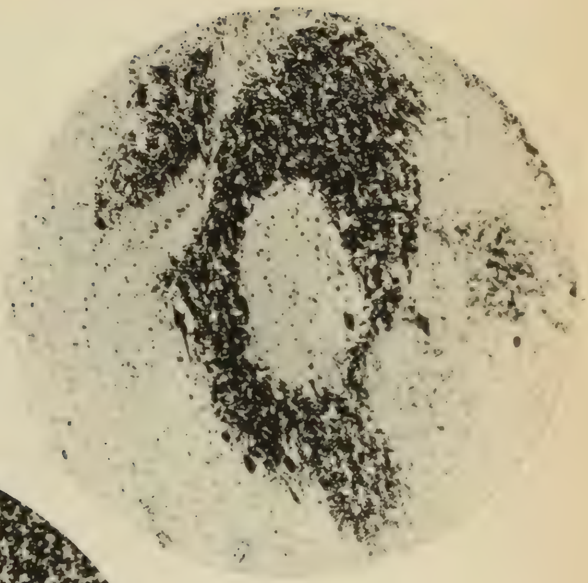
Southard.

Cerebellum.



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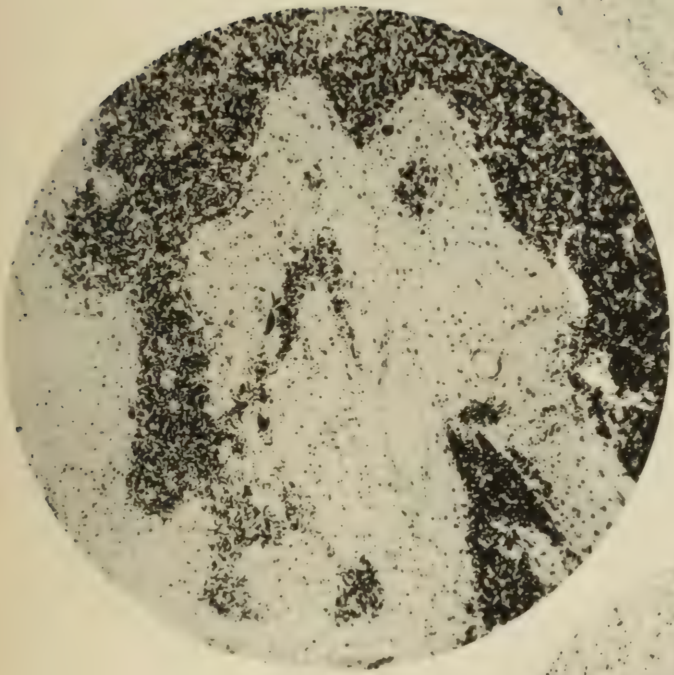

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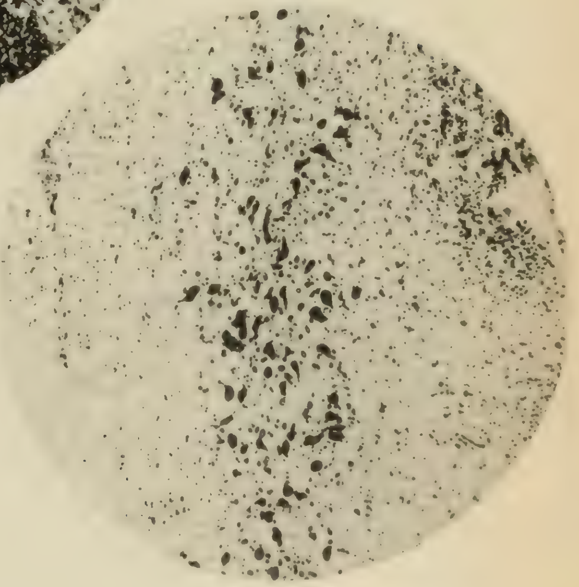

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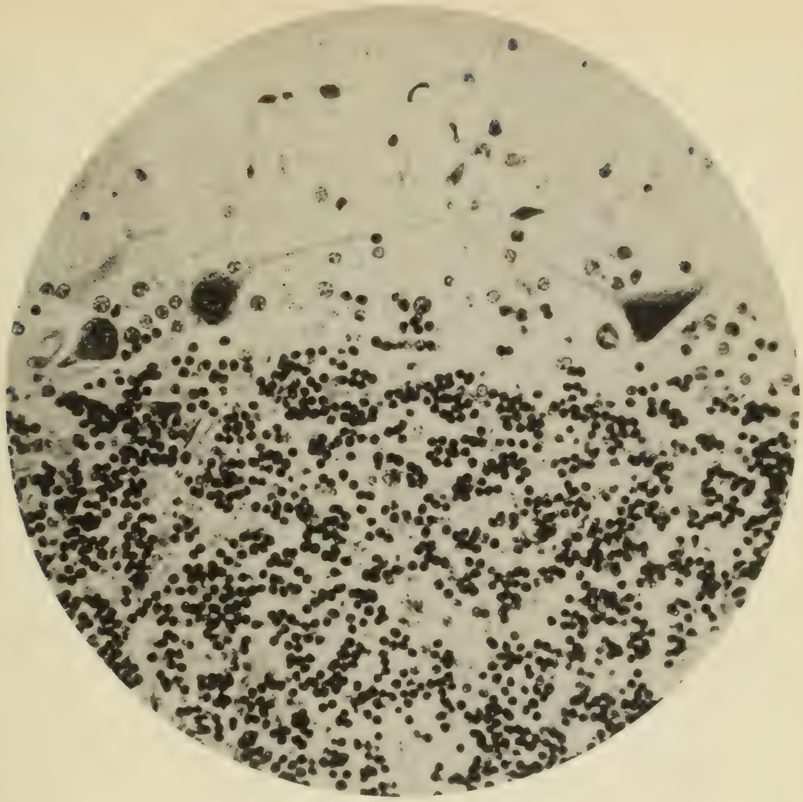

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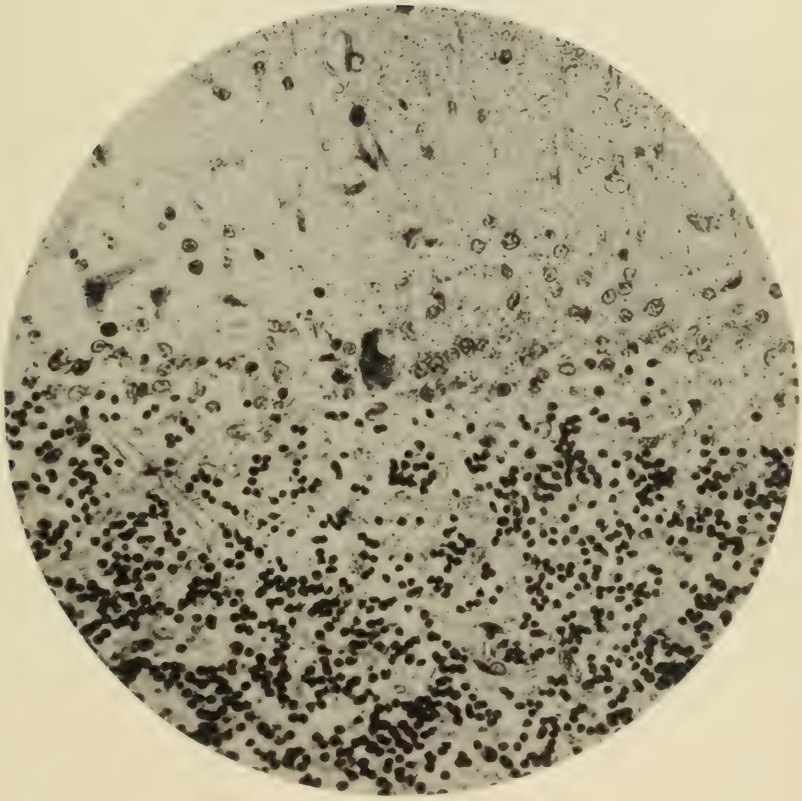

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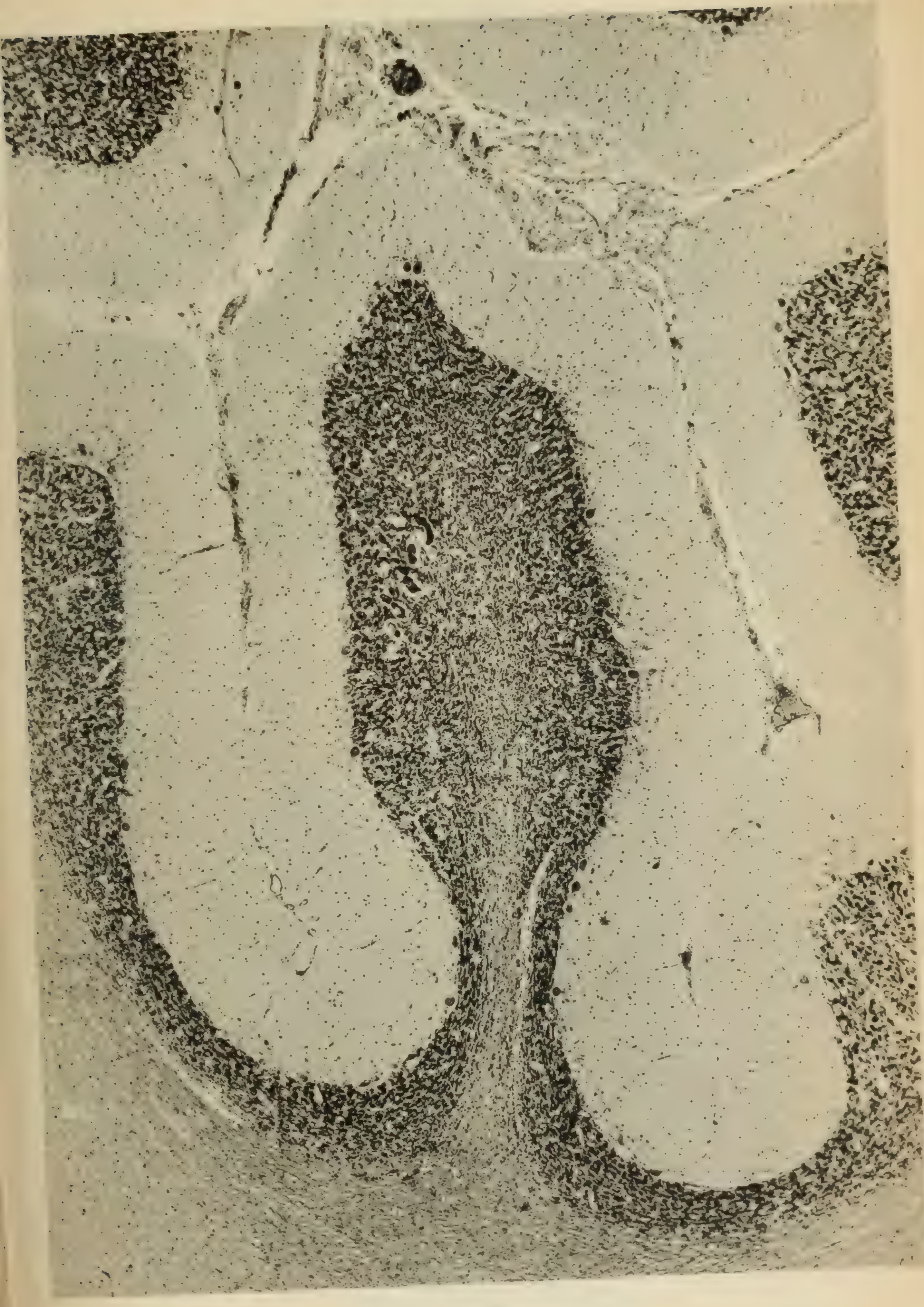

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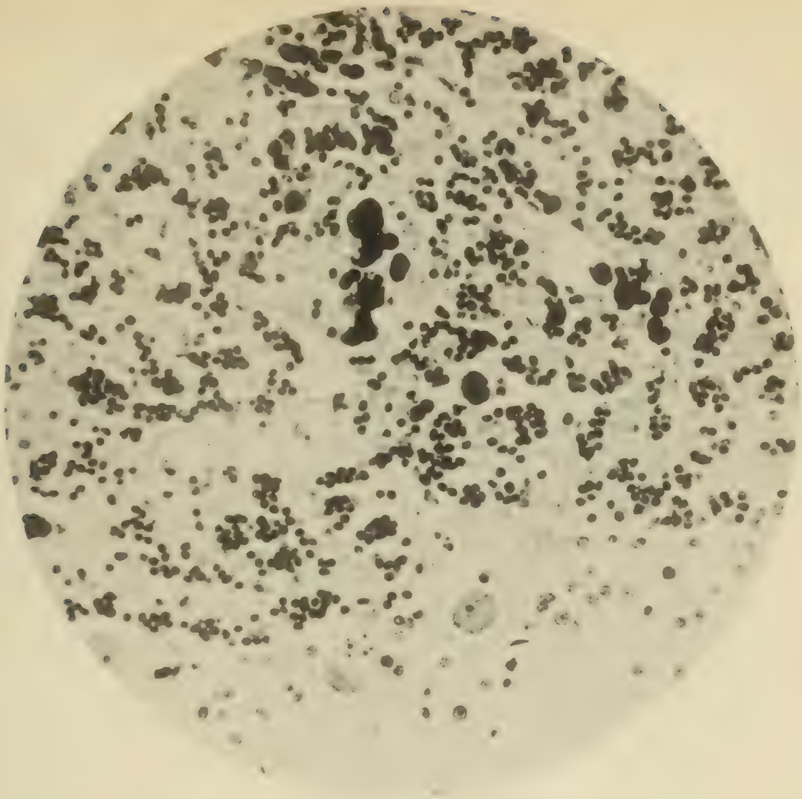
Cerebellum.



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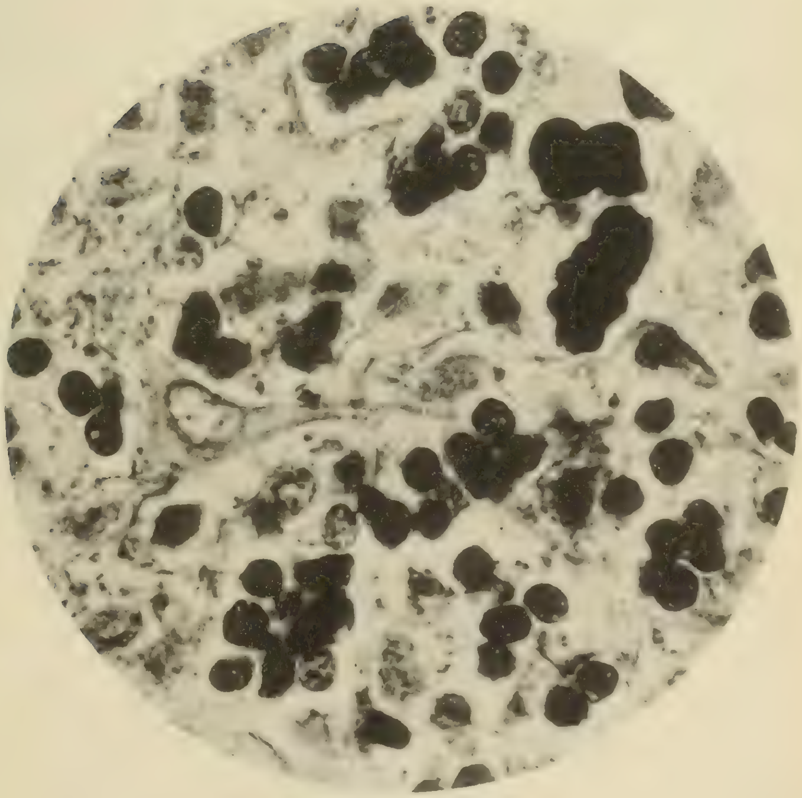

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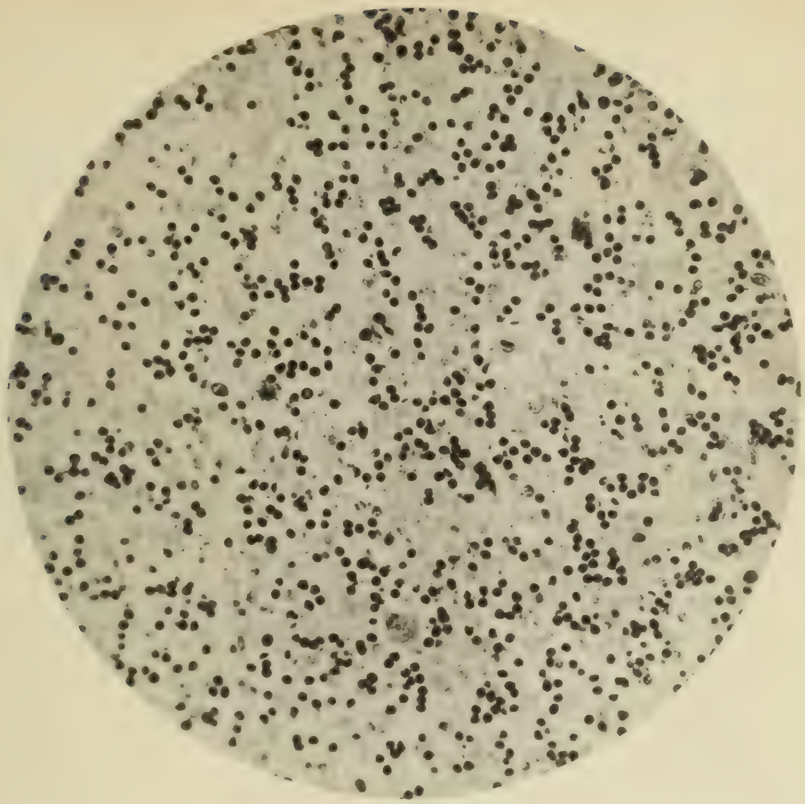
Cerebellum.



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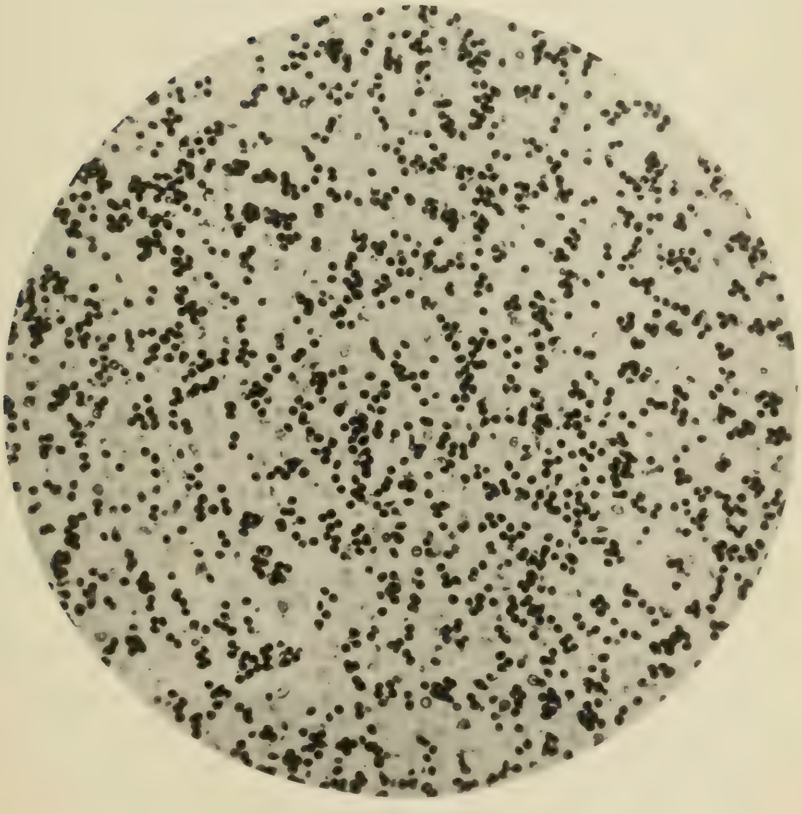

13

Cerebellum.

Southard.

ON SERUM ANAPHYLAXIS IN THE GUINEA-PIG

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Reprinted from

THE JOURNAL OF MEDICAL RESEARCH, VOLUME XVI., NO. 2

(New Series, Vol. XI., No. 2), pp. 143-180, May, 1907

BOSTON
MASSACHUSETTS
U.S.A.

ON SERUM ANAPHYLAXIS IN THE GUINEA-PIG.*

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Animals may react to certain toxic or foreign substances in one of two ways, either by an increased resistance or immunity, or by an increased susceptibility or anaphylaxis.† The reactions of immunity have been demonstrated not only by the increased resistance of the treated animal but also by the occurrence of specific anti-bodies in its blood. Far less is known of the nature of anaphylaxis. Our conceptions of immunity and anaphylaxis presuppose that certain changes have taken place in the somatic cells; theories of animal reaction have been founded on such supposed cell changes, although we possess, in reality, no definite information as to their nature. The present study brings out the mechanism of a striking instance of anaphylaxis and throws light on a definite cell pathology consequent upon the general condition of increased susceptibility.

Attention has been drawn by Otto[2] to a remarkable toxic phenomenon in guinea-pigs. Otto's work was carried out in

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* This study has been facilitated by a grant from the Proctor Fund of Harvard University. Received for publication March 28, 1907.

† This word was first used by Richet[1] to designate the increased susceptibility to a poison from Actinians shown by dogs and rabbits which had survived a small dose of this toxic substance.

the Serum Institute at Frankfort, Germany, following an oral communication to Ehrlich on the part of Theobald Smith. Rosenau and Anderson,[3] working independently of Otto, brought out shortly afterward an extensive monograph which confirmed and elaborated the findings of the German investigator. Circumscribed and definite as the phenomenon appears, it is not easy to follow its evolution. The reaction, as shown by the work of Otto and of Rosenau and Anderson, is somewhat as follows: The injection of any convenient amount of horse serum subcutaneously or intraperitoneally in normal guinea-pigs produces no ill effect. If, however, guinea-pigs are given a very small dose of horse serum, *e.g.*, .0001 to .1 cubic centimeter, and ten days or two weeks are allowed to elapse, a second injection of a relatively large amount, *e.g.*, five cubic centimeters, will cause violent and characteristic symptoms, followed almost invariably by death within the hour. This reaction to a second large dose of horse serum was first noted in guinea-pigs which had survived a diphtheria toxin-antitoxin mixture; but the acquired susceptibility to the serum is in no way dependent on the presence of diphtheria toxin in the first, or "sensitizing," dose, but on the small amount of horse serum which contains the antitoxin.

The literature of immunity bristles with instances of an increased specific susceptibility in animals which have resisted doses of toxic or even apparently non-toxic substances. A list of many such phenomena, more or less closely allied to this serum disease of guinea-pigs, has been given both by Otto and by Rosenau and Anderson. It is of interest to note that explanations of this hypersensitivity are almost as numerous as the instances which have been described; in certain well-studied cases numerous theories exist; for example, there are at least five well-maintained hypotheses concerning the toxic effect of tuberculin in tuberculous animals. The serum disease of guinea-pigs, which we are now considering, apart from its intrinsic interest, offers particularly advantageous conditions for the study of a reaction in the animal body which we believe has not as yet been recognized, and which would appear to be of considerable importance.

In a preliminary consideration of this serum intoxication phenomenon under the simplest conditions, it will be necessary to restate briefly some of the factors which have already been noted by the observers who have preceded us. In fact, n the first phase of this study, only one new fact stands out, namely, an almost constant finding of definite lesions, which esions had been overlooked both by Otto and by Rosenau and Anderson. In our experiments young normal guinea-pigs have been used which weighed at the beginning of treatment from one hundred and fifty to two hundred and fifty grams. The serum both for sensitizing and for toxic effect has been from normal horses, and has been taken aseptically, preserved in sterile bottles without the addition of an antiseptic, and kept at 0° C. until used. It was found by Rosenau and Anderson that a dose of horse serum so small as .00001 or even in one instance .000001 of a cubic centimeter sufficed to render guinea-pigs sensitive to the subsequent toxic dose of serum; it has not concerned us to define so precisely the minimal dose necessary, but we have used in nearly all our experiments an arbitrarily chosen dose of .01 cubic centimeter administered subcutaneously or ntraperitoneally. As a period of incubation we have found t better to wait at least the fourteen or fifteen days advised by Otto. The animals remain sensitive for an undetermined period, at least for many months. For the second toxic dose, five cubic centimeters of horse serum intraperitoneally are necessary to cause death, although much smaller doses will produce characteristically severe symptoms; when njected subcutaneously a considerably larger dose is necessary.

An animal treated as has been outlined, on receiving the second dose of serum intraperitoneally, shows some or all of the following symptoms, and dies, in the majority of the cases, within an hour. In from two to fifteen minutes after injection may be noted twitching of the ears or body, coughing, retching, and less frequently general muscular contraction, with "bucking" and rushing about the cage; after the period of irritation, paralytic symptoms intervene, the animal squats, or feebly drags itself about the cage, complains querulously, shows respiratory distress, and finally falls on its side. This comatose period may last for some time until death intervenes, or the exitus may be precipitated by violent general spasms. The heart beats for some time after the cessation of respiration. Either the irritative or the paralytic symptoms may predominate. An animal may recover after having passed through most characteristically severe phases of both. Death is not a necessary criterion of the complete evolution of the disease, or of the presence of the characteristic lesions; severe symptoms, however, whether followed by death or recovery, are almost invariably accompanied by definite macroscopic findings at autopsy.

Hemorrhage, rather definitely localized, is the characteristic gross lesion in this acute disease. The hemorrhages may be found in one or in several organs; gastric hemorrhage occurs in the majority of cases. The summary which follows indicates the percentage of cases in which lesions occur, and the localization of these lesions. Forty-one guinea-pigs which were examined seriatim fall into two categories: those pigs which died as the result of the disease, and those animals which after having suffered severe and characteristic symptoms were on the road to recovery, or had fully recovered, and were chloroformed within twenty-four hours.

1. Guinea-pigs which died of serum intoxication, twenty-nine animals. Hemorrhage present in twenty-three cases; hemorrhage absent in six cases.
2. Guinea-pigs chloroformed within twenty-four hours after severe symptoms, twelve animals. Hemorrhages present in eleven cases; hemorrhages absent in one case.

Gastric hemorrhages were present in thirty-two of the forty-one cases. Hemorrhages were localized in other organs as follows: cecum in ten cases; lungs, nine cases; spleen, seven cases; adrenal, six cases; heart, three cases;

pericardium, two cases; diaphragm, two cases; lymph glands, two cases; liver, kidney, thyroid, and muscle, each one case.

As has been noted, severe symptoms, irrespective of the subsequent occurrence of death, are sufficient to indicate the evolution of a disease accompanied by definite hemorrhages. It is seen that gastric hemorrhage is a most common but not necessarily constant finding in the well-marked disease. A list of the control animals which have been used to limit these lesions to the disease entity will be given in connection with the microscopic study. It should be noted in this place, however, that the occurrence of hemorrhage in the abdominal organs is not due to the fact that most of the injections were intraperitoneal since the same results are obtained by subcutaneous injections. A detailed description of the macroscopic appearances of these hemorrhages, apart from the gastric and cecal lesions, is hardly necessary; they are minute in general, rather larger in the lungs and spleen than elsewhere. In the stomach the localization is of importance; the lesions which may be one, or two, or multiple, vary in size from a pin point to one or two centimeters in diameter and occur characteristically midway in the greater curvature or in lines diverging from this point, either toward the extremities of the viscus or encircling it toward the middle point of the lesser curvature; they do not occur at the pylorus, in our experience, and are therefore to be differentiated from the lesions described recently by Rosenau and Anderson[4] as caused by diphtheria toxin. In milder grades of lesion the hemorrhages are merely submucous; but in the more advanced stages there is definite erosion, and the stomach may contain clots of blood. The cecal hemorrhages occur about or in the agminated follicles.

We do not wish to insist on the gastric hemorrhages, which occur so frequently in this disease, as anything more than the localized manifestation of a general reaction. They are of interest as stomach lesions produced experimentally without direct injury, and, when studied more minutely, throw light on the evolution of the disease itself.

When we examine more attentively the factors necessary to produce this striking and acute disease the two most salient points are the extremely small dose necessary to sensitize and the existence of a period of incubation. It would be noted by the most casual observer that this incubation period of from ten to fifteen days corresponds to a nicety to the period necessary for the maximal production of an antitoxin after the injection of a toxin, or of a cytolysin after injection of cellular elements. The surprisingly small amount necessary to sensitize need not preclude the formation of anti-bodies during this time, for analogous instances of minute doses of blood leading to the production of a hemolysin are on record. And it is perhaps this corresponding incubation period, more than any other factor, which has led Rosenau and Anderson to a tentative but, as it would seem, incorrect explanation of this phenomenon. These authors believe that the toxic reaction caused by the second dose of serum is due to an interaction between anti-bodies which have been formed against the sensitizing dose and certain toxic substances present in horse serum; they have further assumed, on no certain experimental grounds, that the sensitizing and the toxic substance in horse serum are identical, an assumption in reality necessary to maintain their interaction hypothesis.

Otto has noted that a large initial dose does not cause the sensitivity which regularly follows the usual small dose. Similar results have been indicated by the experiments of Rosenau and Anderson. To these authors such a finding would correspond to other experiments which in their hands seemed to them to prove that repeated doses of serum at short intervals give rise to an immunity. That is, a small amount of horse serum sensitizes guinea-pigs, a large amount, in a single or multiple dose, seems to immunize. If one experiments only so far as Rosenau and Anderson and is dominated by classical examples of the formation of anti-bodies, such a conclusion might be drawn; but if we consider such experiments more exhaustively, a wholly different conclusion emerges. It may be shown, as is evidenced by he following experiment, that a single large initial dose gives rise, not to immunity, but to a temporary insusceptibility which is later followed by characteristic sensitivity.

Experiment 1 — Normal guinea-pigs of similar weight were separated nto two lots and injected intraperitoneally with:

Lot A, 8 cubic centimeters of horse serum.

Lot B, .01 cubic centimeter of horse serum.

The comparative susceptibility of these pigs to a toxic dose of horse erum (5 cubic centimeters) was tested at the following periods:

After 20 days: A pig, No. 1, weight, 365. Slight nervous symptoms.

After 20 days: A pig, No. 2, weight, 385. Slight nervous symptoms.

After 20 days: B pig, No. 1, weight, 380. Dead, 24 minutes. Diaphragmatic and gastric hemorrhages.

After 20 days: B pig, No. 2, weight, 300. Dead, 20 minutes. Small gastric hemorrhages, hemopericardium.

After 36 days: A pig, No. 3, weight, 385. Marked symptoms for four hours. Recovered.

After 45 days: A pig, No. 4, weight, 485. Dead, 40 minutes. Hemorrhage into stomach and lungs.

After 45 days: A pig, No. 5, weight, 395. Dead, 45 minutes. Hemorrhage into stomach.

The conclusion from such an experiment may, for the moment, be stated simply as follows: the injection of a arge initial dose of horse serum delays the period of ncubation necessary to produce sensitivity beyond the period when a small dose is employed.

As has been stated, Rosenau and Anderson have shown hat repeated injections of moderate doses of horse serum nto guinea-pigs at short intervals are followed by no reaction and by an apparent state of immunity or resistance o the toxic dose of serum. Their own experiments should have pointed to the possibility of a different conclusion. As a matter of fact, if a good sized injection (two to five cubic centimeters) is repeated every few days for a few times and then two weeks or even longer allowed to elapse, the subsequent injection of a dose that would cause severe symptoms or death in a properly "sensitized" pig (*i.e.*, one having received a single small initial dose) produces no symptoms. If, however, one waits several weeks, such apparently "immune" pigs become sensitive to reinjection, the degree of sensitivity varying directly with the time elapsed since the last injection and with the total amount of serum previously injected.

The histories of the following guinea-pigs show the absence of reaction to repeated doses of horse serum given at short intervals. These animals were injected with from two to five cubic centimeters of horse serum at intervals, which, in days, are represented by the numerals.

G.P. A. Injected at intervals of 1, 2, 2, and 2 days. No symptoms.
G.P. B. Injected at intervals of 1, 2, 2, and 2 days. No symptoms.
G.P. C. Injected at intervals of 1, 2, 2, 2, and 13 days. No symptoms.
G.P. No. 1. Injected at intervals of 10, 9, 13, 4, and 4 days. No symptoms.
G.P. No. 2. Injected at intervals of 2, 9, 10, 4, and 4 days No symptoms.
G.P. No. 3. Injected at intervals of 9, 9, 13, 4, and 4 days. No symptoms.
G.P. No. 4. Injected at intervals of 9, 9, and 13 days. No symptoms.
G P. No. 5. Injected at intervals of 2, 9, and 13 days. No symptoms.

When, however, some of the above animals were kept for longer intervals after the treatment recorded and then injected, the following results were obtained:

G.P. No. 3. Injected 38 days after treatment above. Distinct symptoms.
G.P. C. Injected 48 days after treatment above. Slight symptoms.
G P. No. 4. Injected 55 days after treatment above. Very severe symptoms. Recovered.
G.P. No. 2. Injected 82 days after treatment above. Very severe symptoms. Recovered. G.P. No. 2 was chloroformed after 4 hours continuous symptoms, and at autopsy typical gastric hemorrhages were found.

Animals that have received one large dose or multiple doses may be referred to as "refractory," and that such refractory animals are at no period really immune to horse serum may be shown in several ways. This condition of ventual susceptibility might be thought to be allied to such onditions as the susceptibility of certain diphtheria or tetanus ntitoxin animals to relatively small doses of their respective oxins; such animals present the curious paradox of free ntitoxin in the blood and diminished resistance of the ssues. The case is not analogous because these refractory uinea-pigs do not produce an antitoxin to the toxic subance in horse serum.

Experiment 2. — Guinea-pig No. 5, which had received five injections horse serum (total, 12 cubic centimeters), was bled ten days after e last injection. A normal guinea-pig was also bled. To nine cubic ntimeters of the respective sera, No. 5 and normal, was added five cubic ntimeters of horse serum, and the mixtures left over night at room mperature. There was a distinct precipitate in the G.P. No. 5 + horse rum mixture which was removed by centrifuging. Guinea-pigs, sentized by the injection of .1 cubic centimeter horse serum forty days eviously, were injected with the mixtures:

G.P. No. 8, weight, 585, given mixture (Serum G.P. No. 5 + horse serum).
G.P. No. 6, weight, 625, given mixture (Serum Normal + horse serum).
G.P. No. 8. Dead in 45 minutes (gastric and cecal hemorrhages).
G.P. No. 6. Very severe symptoms; recovering 5 hours; chloroformed. (Gastric hemorrhages.)

Repetitions of such an experiment always show that the erum of a guinea-pig which has received several injections f horse serum and has been bled at the critical antitoxin eriod (and also at a period when the animal is resistant to e toxic effect of horse serum) contains no anti-bodies hich neutralize the toxic substance in horse serum. Such efractory guinea-pigs frequently show at this period preipitins for horse serum.

Although the blood of refractory animals contains no antiody for the toxic element of horse serum, we might at least nagine that the sensitizing substance of the serum is neutrazed in the body. We might even imagine that such guineaig serum contains an anti-sensitizing substance; this finding, owever, would be difficult to explain in view of the eventual ensitization of the refractory pigs. In fact we find that the serum of refractory pigs, at a period when the animals are resistant to horse serum, not only does not contain anti-sensitizing substances, but *actually contains that substance of horse serum which sensitizes guinea-pigs.*

Experiment 3. — Normal guinea-pigs of similar weight were injected subcutaneously with the same amount of serum of other guinea-pigs which had been treated as follows:

G.P. No. 53. Given subcutaneously 1.5 cubic centimeters serum normal guinea-pig "X."

G.P. No. 75. Given subcutaneously 1.5 cubic centimeters serum normal guinea-pig "Y."

G.P. No. 76. Given subcutaneously 1.5 cubic centimeters serum normal guinea-pig "Z."

G.P. No. 82. Given subcutaneously 1.5 cubic centimeters serum refractory pig "A."

"A" was bled 10 days after receiving the last of 5 injections horse serum. (Total, 13 cubic centimeters.)

G.P. No. 86. Given subcutaneously 1.5 cubic centimeters serum refractory pig No. 4.

No. 4 was bled 19 days after the last of 5 injections horse serum. (Total, 27 cubic centimeters.)

G.P. No. 50. Given subcutaneously 1.5 cubic centimeters serum refractory pig "B."

"B" was bled 11 days after the last of 5 injections horse serum. (Total, 9 cubic centimeters.)

G.P. No. 51. Given subcutaneously 1.5 cubic centimeters serum refractory pig "C."

"C" was bled 14 days after the last of 7 injections horse serum. (Total, 17 cubic centimeters.)

G.P. No. 54. Given subcutaneously 1.5 cubic centimeters serum refractory pig No. 1.

No. 1 was bled 9 days after the last of 6 injections horse serum. (Total, 16 cubic centimeters.)

After 15 days these pigs were given each 5 cubic centimeters of horse serum into the peritoneal cavity with the following results:

G.P. No. 53, No. 75, No. 76. (Controls.) No symptoms.

G.P. No. 82. Severe symptoms. Recovering 2½ hours. Chloroformed. Gastric hemorrhage.

G.P. No. 86. Marked symptoms. Recovered.

G.P. No. 50. Severe symptoms. Recovered.

G.P. No. 51. Dead in 90 minutes. (Diaphragmatic and splenic hemorrhages.)

G.P. No. 54. Dead in 45 minutes. (Gastric and renal hemorrhages.)

There is further evidence that guinea-pigs refractory to horse serum still contain the sensitizing substance of the serum unneutralized. The offspring of refractory animals, born at a period when the mother is resistant to the toxic action of horse serum, *are sensitive, not resistant.*

1. Guinea-pig "C," two days after the sixth injection of horse serum (total, 12 cubic centimeters), had one young (No. 26). When six weeks old this offspring was given five cubic centimeters horse serum intraperitoneally. Very severe symptoms. Recovered. Chloroformed after eighteen hours. Two hemorrhagic erosions of stomach.
2. Guinea-pig No. 4, three days after receiving last of four injections of horse serum (total, 17 cubic centimeters), had three young. Of these offspring two were injected as follows:
   No. 42. (Seven weeks old), five cubic centimeters horse serum *subcutaneously.* Severe symptoms. Recovering one hour. Chloroformed. Several small gastric hemorrhages.
   No. 43. (Nine weeks old), five cubic centimeters horse serum intraperitoneally. Very severe symptoms. Recovering two and one-half hours. Chloroformed. Pin-point hemorrhages of cecum. Small gastric hemorrhages.

There is an analogy between these last experiments on the transmission of sensitivity to offspring from refractory mothers and certain experiments of Rosenau and Anderson[5] and of Anderson;[6] these authors found that the young of sensitized guinea-pigs were also sensitive to horse serum. It was only a step further for us to demonstrate that normal pigs may be rendered sensitive to horse serum by injecting them with the serum of sensitive pigs and awaiting the proper incubation.

Experiment 4.—This experiment was carried on synchronously with Experiment 3, and they therefore supplement and control one another. Normal guinea-pigs were injected subcutaneously with the same amount of sera of other guinea-pigs treated as follows:

G.P. No. 48. Given 1.5 cubic centimeters serum of sensitized pig No. 14. (No. 14 was bled 16 days after receiving .01 cubic centimeter horse serum.)

G.P. No. 49. Given 1.5 cubic centimeters serum of sensitized pig No. 33. (No. 33 was bled 14 days after receiving .01 cubic centimeter horse serum.)

G.P. No. 77. Given 1.5 cubic centimeters serum of sensitized pig No. 61. (No. 61 was bled 29 days after receiving .01 cubic centimeter horse serum.)

The actual sensitivity of these pigs, 14, 33, and 61, was controlled by injecting parallel animals, which had been sensitized the same day, with a toxic dose of horse serum within 24 hours of the time of bleeding their fellows. In each control death occurred in the characteristic manner.

After fifteen days pigs 48, 49, and 77 received each 5 cubic centimeters horse serum intraperitoneally with the following results:

G.P. No. 48, slight symptoms.
G.P. No. 49, severe symptoms.
G.P. No. 77, symptoms. Chloroformed after four hours. No gastric hemorrhage.

It would seem sufficiently astounding that 1.5 cubic centimeters of the serum of a guinea-pig which had received .01 cubic centimeter of horse serum twenty-nine days previously contains sufficient horse sensitizing substance to sensitize a normal guinea-pig to the toxic action of horse serum; the question, however, properly arises whether such guinea-pigs, which remain sensitized so long, uniformly contain substances in their blood which will sensitize normal pigs. An experiment directly bearing on this question follows:

Experiment 5. — There came into our hands, through the courtesy of Dr. P. A. Lewis, three guinea-pigs which had been treated several months previously with a toxin-antitoxin mixture. These animals had the following histories as regards previous injection of horse serum (diphtheria antitoxin).

G.P. No. 4446.	Received .005 antitoxin 204 days previously.
G.P. No. 4452.	Received .003 antitoxin 204 days previously.
G.P. No. 4583.	Received .01 antitoxin 169 days previously.

These animals were bled for a small amount from the carotid and a few hours later two of them were injected into the peritoneal cavity each with 5 cubic centimeters of horse serum, to prove their sensitivity. The results of these injections were:

G.P. No. 4446.	Dead in 35 minutes.	Gastric hemorrhages.
G.P. No. 4583.	Dead in 55 minutes.	Small gastric hemorrhages.

Normal guinea-pigs were injected as follows:

G.P. No. 108. Given subcutaneously 1.5 cubic centimeters serum from G.P. No. 4452.
G.P. No. 109. Given subcutaneously 2.5 cubic centimeters serum from G.P. No. 4446.

G.P. No. 110. Given subcutaneously 2.5 cubic centimeters serum from G.P. No. 4583.

Fifteen days later these pigs were given 5 cubic centimeters horse serum into the peritoneal cavity with the following results:

G.P. No. 108. Dead in 12 minutes. Hemorrhage of spleen and lungs.

G.P. No. 109. Dead in 60 minutes. Hemorrhage of stomach and lungs.

G.P. No. 110. Dead in 12 minutes. Hemorrhage of the lungs.

It is evident from these experiments that sensitivity in guinea-pigs treated with horse serum is accompanied by the constant presence of a substance in their blood which will sensitize other guinea-pigs to the toxic action of horse serum. It would not seem necessary to assume that this sensitizing substance, in the serum of sensitized pigs, is other than the sensitizing substance of horse serum, which has remained unneutralized in the guinea-pig body. The resistance of this substance for many months in a foreign organism is surprising, but diminution might occur to a marked extent and still leave enough to sensitize a normal pig; Rosenau and Anderson have noted that only .000001 cubic centimeter is necessary to produce sensitivity in the first place. Sensitivity would appear to depend upon the presence of this unneutralized substance of horse serum, and for this reason we suggest the name of ANAPHYLACTIN for this body.

Efforts were made to determine whether other recognizable substances of horse serum also remain in the bodies of sensitized or refractory pigs. For this purpose the sera of the animals used to transmit sensitization in Experiments 3 and 4 were tested with a potent anti-horse serum from the rabbit. One cubic centimeter of this rabbit-anti-horse serum readily gave a precipitate with .001 cubic centimeter of horse serum; the serum, however, gave no precipitate with .05, .1 or .5 cubic centimeter of sera from sensitized pig No. 33 and from refractory pigs B, C, and 4. The serum of guinea-pig No. 4, on the contrary, gave a precipitate with horse serum, showing the presence of a precipitin for horse serum.

When we consider the remarkable persistence of horse anaphylactin in the guinea-pig body, the possibility of an actual increase of this substance and not a mere resistance suggests itself. Such an increase might further be suggested by a comparison of Experiments 4 and 5 where the transmitted sensitivity would seem greater in the latter instance where the incubation period was longer. Experiments to throw light on this point were carried out in the following manner:

Experiment 6. — This experiment supplements Experiments 3 and 4, and was performed synchronously. Normal guinea-pigs were injected as follows:

G.P. No. 77. Given 1.5 cubic centimeters serum sensitized pig No. 61. (See Experiment 4.)
G.P. No. 78. Given .1 cubic centimeter serum sensitized pig No. 61.
G.P. No. 79. Given .01 cubic centimeter serum sensitized pig No. 61.
G.P. No. 82. Given 1.5 cubic centimeters serum refractory pig A. (See Experiment 3.)
G.P. No. 84. Given .1 cubic centimeter serum refractory pig A.
G.P. No. 85. Given .01 cubic centimeter serum refractory pig A.

On injection, fifteen days later with 5 cubic centimeters horse serum, these animals reacted as follows:

No. 77. Symptoms. Chloroformed four hours. No visible lesions.
No. 78. Slight symptoms. Chloroformed four hours. No lesions.
No. 79. No symptoms. Chloroformed four hours. No lesions.
No. 82. Severe symptoms. Chloroformed three hours. Gastric hemorrhages.
No. 84. Severe symptoms. Chloroformed four hours. Gastric and pulmonary hemorrhages.
No. 85. No symptoms. Chloroformed four hours. No lesions.

This experiment would indicate quantitatively two things: First, that the blood of the refractory pig contains more anaphylactin than the blood of the sensitized pig, which is a priori evident from the much larger amount of serum received by the refractory pig; and secondly, that the degree of transferred anaphylaxis varies with the amount of the serum used in transferring the sensitivity to a second animal.

It may further be shown that anaphylaxis cannot be transferred to a third order of animals.

Experiment 7. — Guinea-pigs No. 80 and No. 83 were treated exactly as animals 77 and 82 respectively in the last experiment, that is, they were sensitized by transfer of serum from a sensitized or a refractory pig. Normal guinea-pigs were injected as follows:

G.P. No. 111. Given 2.5 cubic centimeters serum from pig No. 80.
G.P. No. 112. Given 2.5 cubic centimeters serum from pig No. 83.

Fifteen days later these pigs were given 5 cubic centimeters of horse serum intraperitoneally. No symptoms.*

This shows that anaphylaxis, with the doses used, cannot be transmitted beyond the first transfer. This non-transference depends on too great dilution of the original anaphylactin in the animal body. It therefore seems evident that the anaphylactin of horse serum remains simply unneutralized and does not increase in amount in the guinea-pig.

Before considering the evolution of the serum disease more in detail it is important to determine if possible the identity or non-identity of the anaphylactin with the toxic element of horse serum. Such a determination presents a serious experimental difficulty. It has been shown that serum of refractory pigs No. 1 or C could sensitize normal guinea-pigs (Experiment 3); it was therefore of interest to determine if these sera would intoxicate properly sensitized pigs.

Experiment 8. — G.P. No. 55 (sensitized by injection twenty-six days previously of .01 cubic centimeter horse serum) was given 5 cubic centimeters serum of guinea-pig No. 1 intraperitoneally. No symptoms.

G.P. No. 56 (sensitized as No. 55) given 3.5 cubic centimeters serum of guinea-pig C. No symptoms.

This experiment may well be regarded as inconclusive as far as proving the non-identity of anaphylactin and toxic substance, on account of the wide divergence in doses necessary to produce anaphylaxis on the one hand and intoxication on the other. In order to demonstrate more conclusively that the anaphylactin and the toxic substance are not identical, another method of administering the toxic dose must be mentioned. It was found that sensitized guinea-pigs are killed by very small doses of horse serum if it be given directly into the circulation. Normal pigs, however, are unaffected by a relatively large dose. The experiment follows:

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* Another guinea-pig (No. 113), given 3.5 cubic centimeters serum from pig No. 80 and injected with five cubic centimeters horse serum intraperitoneally after thirty days also showed no symptoms.

Experiment 9. — 1. Normal guinea-pig, weight, 300 grams. Given 1 cubic centimeter horse serum into right carotid. No symptoms. Chloroformed 3 hours. No lesions.

2. Sensitized G.P. No. 95, weight, 340 grams. Given 1 cubic centimeter horse serum into right internal jugular. *Dead in* 3 *minutes.* Lungs studded with pin-point hemorrhages. Numerous hemorrhages into heart muscle.

3. Sensitized G.P. No. 93, weight, 350 grams. Given .5 cubic centimeter horse serum into right carotid. Dead in 4 minutes. One small hemorrhage on surface of brain. Numerous oozing hemorrhages of lungs which increase under observation. Smaller hemorrhages of heart.

4. Sensitized G.P. No. 98, weight, 360 grams. Given .05 cubic centimeter horse serum into right carotid. Dead in 10 minutes. Small hemorrhages of lungs. Splenic hemorrhages.

5. Sensitized G.P. No. 29, weight, 590 grams. Given .02 cubic centimeter horse serum in right carotid. Marked symptoms for an hour. Chloroformed. Gastric hemorrhages. Small lung hemorrhages.

6. Sensitized G.P. No. 35. Given .005 cubic centimeter. Very slight symptoms. Chloroformed 2 hours. No lesions.

7. Sensitized G.P. No. 97. Given 1.5 cubic centimeters serum refractory pig No. 4. (See Experiment 3.) No symptoms.

(Guinea-pigs 93, 95, 97, 98 had all been sensitized with .01 cubic centimeter 30 days previously. Nos. 29 and 35 had been sensitized with 3 cubic centimeters 60 days previously.)

This experiment brings out several novel points to which reference will later be made. It is of interest here to note that such tiny amounts of horse serum when put directly into the circulation will cause death or symptoms with lesions. This line of experimentation has been introduced for the purpose of showing that the serum of a refractory pig which contains anaphylactin does not contain any amount of the toxic substance of horse serum as far as can be detected by so delicate a biological method. We feel, therefore, justified in concluding that the anaphylactin and the toxic substances in horse serum are not identical, the one being retained in the guinea-pig body and the other eliminated or destroyed. It would be desirable to attempt a chemical separation of these two elements.

It is already evident from the rapid evolution and often speedy termination, that this disease is due to a sharp reaction which takes place in the body, rather than a cumulative intoxication. The sharpness of the reaction is especially marked if the intracarotid method of giving the toxic dose is employed.

It may further be shown that once this reaction has taken place, the further administration of horse serum produces no effect. If the serum be administered in divided doses within a relatively short space of time, much more than a fatal dose may be given without causing death. An experiment to illustrate follows:

Experiment 10. — Guinea-pigs 94, 95, and 99 had each received .01 cubic centimeter of horse serum fifteen days previously. They were treated as follows:

No. 94, weight, 250 grams. Given 1.5 cubic centimeters horse serum *subcutaneously*.

No. 96, weight, 315 grams. Given 1.5 cubic centimeters horse serum *subcutaneously*.

No. 99, weight, 260 grams. Given 5 cubic centimeters horse serum intraperitoneally.

No. 99. Dead 30 minutes. Lung hemorrhages.

Nos. 94 and 96 became prostrated and were very sick at end of one hour; 94 was then given 5 cubic centimeters horse serum intraperitoneally, but showed no increase of symptoms and recovered in three hours; 96 received 5 cubic centimeters horse serum intraperitoneally 110 minutes after first injection, while still sick. No increase of symptoms. Recovered three hours.

Such experiments show conclusively that the evolution of the disease depends on some rapid reaction or assimilation. When we compare the ways of inoculation of the toxic dose, carotid, peritoneal, and subcutaneous, it is evident that the more quickly the serum comes intimately in contact with the organism the more rapid the evolution, and conversely, the smaller the dose of serum necessary to produce maximal results.

It may further be shown that mere dilution of the toxic dose with isotonic fluids tends to diminish the severity of the reaction. This dilution effect was shown by a guinea-pig which chronologically was placed in the last experiment for the sake of utilizing control pig No. 99.

Guinea-pig No. 92, weight, 230 grams. (Sensitized as 94, 96, 99). Was given 10 cubic centimeters normal saline solution into the peritoneal cavity. One hour later 5 cubic centimeters horse serum was given intraperitoneally. The animal showed symptoms which were never severe and recovered perfectly in two hours.

Numerous further instances of the effect of dilution have occurred in the course of experiments carried out for other purposes. One of these may be cited.

Experiment 11. — This experiment was to demonstrate the presence or absence of anti-bodies for the toxic substance of horse serum in the serum of a rabbit which had received several injections of horse serum. (Rabbit-horse No. 1, injected 5 times with horse serum (total, 19.5 cubic centimeters) during one month, and bled 12 days after last injection. Serum heated to 56° C. for 30 minutes to destroy alexine.)

Mixtures were made of the serum of this anti-horse rabbit and horse serum, and also of the serum of a normal rabbit for control. After contact for 18 hours at room temperature the mixtures were injected into sensitized guinea-pigs. (.01 cubic centimeter 17 days previously.)

G.P. No. 36. Weight 335. Given intraperitoneally mixture (5 cubic centimeters serum normal rabbit 56° + 5 cubic centimeters horse serum).

G.P. No. 37. Weight 305. Given intraperitoneally mixture (5 cubic centimeters serum anti-horse rabbit No. 1, 56° + 5 cubic centimeters horse serum).*

G.P. No. 38. Weight 345. Given intraperitoneally mixture (2 cubic centimeters serum anti-horse rabbit + 5 cubic centimeters horse serum).*

G.P. No. 39. Weight 275. Given intraperitoneally mixture (.55 cubic centimeter serum anti-horse rabbit + 5 cubic centimeters horse serum).

G.P. No. 40. Weight 365. Given intraperitoneally 5 cubic centimeters horse serum.

Results were as follows:

No. 36. Least severe symptoms.
Nos. 37, 38. Severe symptoms.
No. 39. Dead in 25 minutes. Cecal hemorrhages.
No. 40. Dead in 35 minutes. No hemorrhages.

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* Mixture had given slight precipitate which was removed before injection.

This experiment brings out two facts. The serum of a rabbit injected several times with horse serum and bled at the critical time for antitoxins shows no anti-bodies for the toxic substance of horse serum; the non-formation of antitoxins in this experiment was confirmed both with larger doses of the serum of this specific rabbit, and also with varying doses of the serum of another anti-horse rabbit. Of importance for the present, however, is the observation that mere dilution of horse serum with the serum of a specific rabbit or of a normal rabbit decreases the symptomatic disturbance in a sensitive pig.

HISTOPATHOLOGY.

We have devoted much time to the histopathological side of the work. Despite the volume and quality of the requisite controls, we are enabled to draw a number of definite conclusions as to the structural character of the lesions found. These conclusions deal in the main with the lesions of the acute disease. We propose to return shortly in a separate paper to a consideration of some characters in the chronic or repeatedly induced disease.

The lesions of the acute disease, striking as they appear to the naked eye, yield much more to microscopic examination, since they not only are more manifold but also offer some points as to the genesis of this group of changes. We have been aided especially in the present study by the Marchi method for fatty degeneration. The crux of the work upon structural details has proved to be the investigation of the gastric mucosa, which affords a peculiarly clear field for the study of fatty changes.

Besides the hemorrhages which may be detected in the gross, there are minute interstitial and oozing *hemorrhages* which can be made out microscopically. At least a portion of these hemorrhages is demonstrably due to endothelial changes in capillaries. We are able to offer a neat histological demonstration of the fatty change which underlies this type of endotheliolysis.

Not all the lesions are capillary or hemorrhagic. *Fatty* *changes* are demonstrable also in voluntary muscle fibers, in heart muscle fibers, and in nerve fibers. The hemorrhages and the above fatty changes are certainly due in some way to the experimental treatment of the guinea-pigs, and we believe them adequately controlled. The liver and the kidney also exhibit fatty changes of a similar appearance and similarly focal; but we have been unable to control the liver and kidney lesions to our satisfaction. Nevertheless, the capillary fatty change in the renal pyramids must be taken as due to the serum injections in some way. There is also a species of alteration in the large nerve cells of the spinal cord and bulb which is in our opinion produced by the treatment; but the nerve cell changes are within the limits of error in staining and are probably secondary, in any event, to the nerve fiber changes.

We have examined formaldehyde-fixed material systematically by the Marchi method[7] for fat, from heart, lung, spleen, stomach, liver, pancreas, kidney, adrenal, cervical lymph nodes, brain, cord, peripheral nerves and muscles from fore and hind limbs, and material incidentally from several other organs. We have supplemented the Marchi method to a limited extent by fresh examination of tissues in glacial acetic acid and by staining with Scharlach R. The desire for permanent preparations and for appearances which would photograph well with high powers has led us to prefer the slower Marchi method for the bulk of the work.

Zenker-fixed tissue, prepared by the eosin and methylene blue method,[8] has proved of service in the study of hemorrhages and alterations in heart and voluntary muscle fibers. The same series of organs and tissues prepared by the Marchi method has been carried through by the eosin and methylene blue method.

Various parts of brain and cord, with (in some instances) dorsal root ganglia, have been fixed in alcohol and stained by Nissl's original methylene blue method.[9]

The most striking feature of both the hemorrhages and the fatty changes in all the affected organs is their *focal distribution.* It is this character which demands such extensive control and comparative work with normal and diseased tissues. This difficulty, however, is less pronounced in the case of the gastric mucosa, in which there normally exists no microscopically visible fat.

We have not been aided to any extent by accounts in the literature of experimental toxic lesions. In fact there is little evidence from published work that the histopathology in these fields is at all thoroughly wrought out. The lesions are, in the nature of things, *not specific.* It is instructive that no single finding in our work fails to find some parallel in other fields. The gastric hemorrhages themselves are found under a great variety of toxic and other conditions; it remains to be seen whether the finer anatomy in other conditions is at all constantly like that described for our own experimentally produced erosions.

We have examined material from forty-five guinea-pigs, prepared directly for this work, as well as considerable other guinea-pig material, especially diphtheria-toxon paralysis material, upon which one of us is working at the suggestion of Theobald Smith. A large number (850+) of microscopic sections accrued from the forty-five guinea-pigs alone. Each guinea-pig requires an average of eleven Marchi preparations.

We separated our material into several classes, as

I. *Control material,* consisting of supposedly normal tissues and tissues from guinea-pigs suffering from other diseases than the one under consideration and including material chiefly over and above the forty-five guinea-pigs directly prepared for the work.

II. *Anaphylaxis material,* consisting of tissues from guinea-pigs at various stages after the initial injection and before a toxic injection. Various intervals were allowed to elapse after the anaphylactic dose in different animals, so that an adequate representation could be got of conditions in the process of anaphylaxis.

III. *Toxic material,* governed in part by the frequent lethal issue, but obtained also at various intervals before death would naturally have supervened and at various intervals subsequent to recovery from toxic symptoms.

IV. *Refractory material*, composed of tissues from guinea-pigs injected with repeated large doses, obtained at intervals corresponding both with the refractory period and with a period subsequent thereto.

Stomach.—We are inclined to attach considerable significance to our findings in the gastric mucosa and vessels. Although it is probable that fatty change in the mucosa and its vessels is far more frequent than we suppose (*e.g.*, in various infections and toxic states), yet there is no reason to believe that fat is of normal occurrence in the gastric mucosa. Our own work indicates that the guinea-pig stomach under normal conditions contains no fat. The anaphylactic material also fails to show fat in the stomach wall. Many parts of the stomach in the toxic material fail to show fat. But the toxic material constantly shows fatty change of a characteristic appearance in various foci (twenty-five out of twenty-six toxic pigs examined). There is no more constant lesion anywhere in the tissues of our toxic material (Plate XII., Fig. 1). The lesion is a focal one. Intervals of tissue without fat adjoin the foci of fatty change (Plate XII., Fig. 2).

The gastric mucosa[10] is a peculiarly clear field for the demonstration of fat. Very little material of any sort can be brought out by osmic acid in the gastric mucosa of guinea-pigs. The granules seen by Langley[11] with the employment of osmic acid, and regarded by him as related with digestion, are not alleged to be preserved in the Marchi method. Nor are these granules of Langley in the gastric epithelium, but rather in the true secreting gland cells of the gastric mucosa. The observation by Volhard[12] of a lipase in the stomach is of interest in this connection. We are not aware that the histology of the action of the gastric lipase has been worked out. Confusion with the cellular fat to which we here call attention could scarcely arise except in work on gastric absorption of fat.

Our own observations of fat in the gastric mucosa are, however, in no way equivocal or possible of confusion with

Langley's granules or with fat which might be seen in the course of absorption. Not only are our controls and anaphylactic stomachs negative for fat by the Marchi method, but also the focality of the lesion in any given stomach, together with the associated congestion and at times erosion of surface, is wholly convincing as to the pathological character of the fat shown.

The gross hemorrhagic lesion of the stomach is in our experience always associated with fat. The fat is found in two places, in the gastric epithelium (Plate XIII., Fig. 3), and in the endothelium of the neighboring vessels (Plate XIV., Fig. 6). We are inclined to regard the hemorrhages as dependent upon rupture of vessels weakened by fatty change. We are inclined to regard the fat of the gastric epithelium (Plate XIII., Fig. 4) as often independent in origin, not associated with vascular lesions. Thus we fail to find hemorrhages without fat in surrounding tissues, and we fail to find endothelial fat without fat in gastric epithelium (Plate XIII., Fig. 5); but gastric epithelial fat does occur as the unique early result of the intoxication. The gastric conditions seem to resemble logically the conditions in heart muscle, where also we find fatty changes in muscle fibers without fat in endothelial linings. In the case of heart muscle, just as in voluntary muscle, we can exclude the dependence of the fatty change in fibers upon alterations of single capillaries.

Heart muscle. — Our work with the heart muscle has concerned the question of fatty change in two tissues, the muscle fibers and the capillary walls.

We recognize that the heart muscle is not a pure field for the investigation of fatty changes. Although microscopically visible fat must be regarded as abnormal in heart muscle fibers, yet we have no adequate idea of the various non-experimental conditions under which microscopically visible fat may develop. The finding of fatty changes in the heart, as in several other organs of the so-called "normal" laboratory animal, is scarcely above suspicion in any single instance. How frequently may mild, incidental, and curable fatty changes occur in various organs, even in man? Even the present work itself tends to show how suddenly the phenomenon of microscopically demonstrable fatty change may be developed under conditions whose intimate nature we do not fully understand.

Nevertheless, our heart muscle findings are second only to the gastric findings in point of reliability. The lots of guinea-pigs employed in the present work have not been found subject to fatty degenerations of the heart muscle of non-experimental origin. Moreover, the anaphylactic material has failed in any instance to show fatty change.

We have therefore been fortunate enough to employ a series of animals in which all the controls were free from fat in heart muscle fibers. Taken in conjunction with the focal fatty changes in capillary walls we feel that our heart findings in toxic material are almost as convincing as the gastric findings, and that they give evidence that the toxic agent takes effect (just as in the stomach) often independently in two different tissues of the same organ.

Numerically, however, heart lesions fail to equal the gastric lesions. Seven out of twenty-six pigs, examined in the toxic phase, failed to show heart lesions of any demonstrable character. An examination of the histories of the seven pigs shows that no conclusion can be drawn as to the general severity of the process from the particular incidence of lesions in the heart. One guinea-pig which showed the most manifold hemorrhages in other organs, including voluntary muscle, failed to show heart lesions of any sort. One guinea-pig, which died a little less than four hours after the second injection and showed unusually severe symptoms, failed to yield heart lesions, though the stomach wall was one mass of hemorrhages.

The maximal examples of heart muscle fiber change have been found in guinea-pigs subject to the repeatedly induced disease; to this topic we hope to return shortly in a separate paper. Nevertheless, we have found in certain pigs subject only to the two usual injections (anaphylactic and toxic) a degree of fatty change comparable to the extensive alterations found in human fatty myocarditis (Plate XV., Fig. 9).

The capillary lesions recall those of the stomach, but are found often without associated hemorrhages or fiber changes. In fact the heart lesions afford a more convincing proof of the double action of the toxic agent (fibrolytic and endotheliolytic) than the stomach lesions. When working with the stomach lesions, we began to doubt whether the lytic phenomena could be logically separated from one another. But in the heart, as also in voluntary muscle and in the nervous system, there is the best evidence of focal changes not only in the associated tissues of a single locus but in disparate tissue elements (Plate XV., Figs. 10 and 11).

There is considerable reason to think that the hemorrhages in the heart, as perhaps in other organs, are due to ruptures of vessels consequent upon endothelial fatty change. It is surprising how difficult this is to prove. Especially in those organs which are continuously in motion, the hemorrhages speedily get beyond the range of the original focus of destruction, and their relation to endothelial changes fails of ready demonstration.

We think that our intracarotid injections with death in four minutes go far to prove the relation of the hemorrhages to endothelial change. Histological examination of the heart in such a case shows fat drops in the endothelium of many capillaries in a hemorrhagic focus.

Voluntary muscle. — It is difficult to get a numerically fair sample of voluntary muscles without carrying technical work out of manageable bounds. Confining our examination to a few muscles from the fore and hind limbs (occasionally from the back or elsewhere), we were surprised to find that fifteen out of twenty-three toxic guinea-pigs examined showed fatty degeneration in one or more muscles of greater or less degree.

The changes found correspond to those found in various febrile diseases and other conditions.[13] They consist of (1) a swelling and disappearance of striations with increase of refractivity in the fiber, and more frequently of (2) the development of rows of smaller or larger fat droplets in the fiber with ultimate loss of markings (Plate XVI., Figs. 12, 13, 14).

The theoretical interest of these changes is chiefly comparative. Even more clearly than the heart fiber changes, these voluntary muscle fiber changes stand out as not secondary to vascular or local changes, but as focal cellular reactions.

Nervous system. — The same adventitious blackenings in myelin sheaths with the Marchi method have been found in our guinea-pig material as have been described so often in published accounts of work with this method.[14] We have attributed no significance to these "normal" black grains, found often, as Singer and Münzer[15] have described them, scattered through the spinal cord or in posterior root zones or in the arcuate fibers or raphe of the medulla. We have also met numerous examples of artificial rupture granules at the points of section of peripheral nerves.

Besides these *granular artefacts*, we find two important changes, 1, a frequent alteration found near nodes of Ranvier (here termed *nodal change*), and 2, the well-known discs or drops occupying the whole of a sheath for some distance (here termed *linear change*).

The linear degenerations are examples of the well developed and comparatively well understood Marchi degeneration, which we are accustomed to study in work on tract degenerations. Only in the present study, where we deal with effects brought about in far less time than is assigned for obtaining frank Marchi degenerations (two to four days), we discover no tract degenerations but rather isolated fiber degenerations (Plate XVII., Fig. 16). There is even a question whether it is proper to term the changes degenerations, since it is wholly probable that fibers with early linear changes may recover their myelin content without definite regeneration brought about through influences from the nervous elements engaged.

In any case, the nodal changes, which can be demonstrated as swelling and fatty transformation of the myelin sheaths on each side of the cleft of Ranvier (Plate XVII., Fig. 15), are changes of so trivial a character that they may well occur, fade, and reoccur many times without detriment to the nerve fibers.

We find focal linear alterations in our toxic material very frequently. They are the rule in the peripheral nerves, often found in entering and departing root fibers in the spinal cord and medulla, and decidedly less often in tissues above the medulla. The anaphylactic material shows very few examples of such linear degeneration. And these instances are not constant.

The nodal changes have a much wider occurrence. We find them not only in the toxic and in the anaphylactic material but also in various other material, even in some so-called " normal " material. We regard these changes as important, although not differential, in serum anaphylaxis or intoxication. They are a sign of the lability of the myelin sheath, which is here accessible to alterations by various agents.

Material from twenty-four toxic-phase guinea-pigs showed fatty alterations either in fore-leg nerves or in hind-leg nerves in nineteen subjects. Very frequently all nerves in a given subject showed the same alterations in fairly even degree throughout. Nine subjects showed the more serious changes which we have termed " linear," together with numerous examples of the " nodal " change. Ten subjects showed the nodal change alone or so few examples of linear degeneration that the findings might seem adventitious.

The question at once arose whether corresponding alterations could be demonstrated in the cells of origin for fibers so affected. Such changes might be a kind of prodrome to an actual " axonal " reaction of Nissl,[16] the well-known phenomenon of granule solution and eccentricity of nucleus which occurs in nerve cells whose axis cylinders have been resected. We believe we have found such prodromata to the axonal reaction in the shape of definite reduction in size of the Nissl bodies in certain cells which might well correspond to the fibers undergoing linear Marchi changes. Definite as these cell changes are, they are within the limit of technical error, and since they are not essential to the present discussion, we shall not go farther into the question at the present time.

To sum up our work on the neuropathological side, we have incidentally described certain myelin sheath changes which we think exemplify the remarkable lability of the myelin sheath ("nodal changes") and have made out in the anaphylactic material an accentuation of these lability changes, together with a trifling tendency to somewhat more serious and extensive changes of the myelin sheath (the well-known changes here termed "linear"). These latter changes, always focal, are displayed in greater numbers in our toxic material. These changes affect the peripheral nerves and the entering or departing root fibers in both cord and bulb. They are always focal, often not numerous, and quite resemble the voluntary muscle and heart muscle changes in focality and numerical variation.

Other organs. — We collected and examined much material from other organs.

Of these the most interesting organs are the kidney and the liver. In these organs occurred numerous focal changes, to which one might attribute significance were it not for their occurrence in "normal" and control material.

The liver shows in a small proportion of cases focal fatty alterations (Plate XIV., Fig. 7). These are, as a rule, not related with the blood supply. In a few instances the liver showed fat in capillary walls.

The kidney showed one remarkable lesion in four out of twenty-four toxic-phase guinea-pigs. The lesion failed to occur in our "normal" and anaphylactic-phase material. The lesion consisted in an exquisite deposit of small droplets of fat in the capillary walls of the pyramid region (Plate XIV., Fig. 8). This phenomenon was the more remarkable because the adjoining tubules were in most cases wholly free from fat. The finding was in so small a proportion of cases that no extreme significance can be attached to it. It assumes logical place, however, with the capillary fat of the stomach and the heart. The peculiar locus of the change is, indeed, suggestive, because, as Dr. Councilman has remarked to us, the renal blood pressure is doubtless lowest in this region.

It is difficult to interpret findings in the lungs. Just as in the case of the heart muscle and the voluntary muscle, so also the lungs, as motile organs, so quickly disseminate a hemorrhage that the originally ruptured vessels may escape section in the embedded tissue. We have found in certain instances a small amount of fat in cells lining alveoli; but little special significance can be attached to these.

We have also paid some attention to fat findings in cells lining the pleura and pericardium. But the fat-containing cells in these loci are so few that their occurrence is of no special importance. Nevertheless, two instances of hemopericardium were noted among gross lesions in the toxic material.

The occurrence of fat-containing cells free in the dilated vessels of the gastric mucosa in toxic material has also a certain interest. In numerous cases the cerebral meninges showed a moderate number of fat-containing cells of the type found in many chronic lesions.

The study of the histopathology of this serum disease shows us that we have to deal with an intimate cell reaction demonstrable by definite cell lesions. We have shown that the blood of sensitized guinea-pigs regularly contains unneutralized anaphylactin, the substance in horse serum which gives rise to anaphylaxis. It would seem that the toxic substance of horse serum, so far as can be determined by biological tests, is not identical with the anaphylactin. There are two possibilities as to the cause of cellular destruction on the administration of the second dose:

First: It is conceivable that a combination between the whole horse serum and the anaphylactin of horse serum in the guinea-pig might give rise to a toxic substance which could destroy the cells.

Second: It is conceivable that the cells have been prepared, possibly by the constant irritation of the foreign unneutralizable substance, anaphylactin, so that a sudden inrush of horse serum overwhelms them.

The first possibility may be submitted to experimental proof. In fact some experiments of Rosenau and Anderson would seem definitely to exclude this conception. These authors showed [17] that mixtures of sensitive guinea-pig serum and horse serum had no toxic effect on normal guinea-pigs. It seemed to us so important to confirm this point that we repeated the experiment in a manner even more conclusive.

Experiment 12. — It has been shown that a sensitive guinea-pig can be given distinct symptoms and characteristic lesions by injecting .02 cubic centimeter of horse serum into the carotid. Normal guinea-pigs were given intracarotid the following mixtures of horse serum and the serum of a sensitive guinea-pig. The mixtures were allowed to stand 30 minutes at 37° C. before injection (no precipitate).

1. Normal guinea-pig "A," weight 325, given into right carotid (horse serum .5 cubic centimeter + serum sensitized pig 1.5 cubic centimeters). No symptoms.
2. Normal guinea-pig "B," weight 285, into right carotid (horse serum .1 cubic centimeter + serum sensitized pig 1.5 cubic centimeters). No symptoms.

This experiment proves that there is no toxic mixture formed by the interaction of the serum of sensitized guinea-pigs (anaphylactin) and horse serum.

By exclusion, we are led to assume that the intoxication in sensitive pigs is due to some change in or preparation of their cells by the sensitizing dose. An hypothesis may be offered which seems to coincide with existent facts; restating in detail our condition, the following explanation may be given of the serum anaphylaxis in guinea-pigs: There is a substance in horse serum (anaphylactin) which is not absorbed by the guinea-pig tissue, is not neutralized, and is with great slowness eliminated from the animal body; many or all of the other substances are assimilated more or less readily by the tissues, are neutralized in a relatively short space of time, and in some instances (precipitogens) definite reaction products to them may be formed. When a normal guinea-pig is injected with a small amount of horse serum the greater part of its elements are rapidly eliminated; the anaphylactin, however, remains and acts as a constant irritant to the body cells, so that their avidity for the other assimilable elements of horse serum, which have accompanied the anaphylactin, becomes enormously increased. At the end of two weeks of constant stimulation on the part of the anaphylactin, and of constantly increasing avidity on the part of the somatic cells, a condition has arrived when the cells, if suddenly presented with a large amount of horse serum, are overwhelmed in the exercise of their increased assimilating functions and functional equilibrium is so disturbed that local or general death may occur. The period of incubation is prolonged, in the case of a large initial dose or of multiple doses, in proportion to the amount of serum injected, because the cell avidity cannot begin to increase until the assimilable substances that have been heaped up are to a large extent eliminated, and the normal assimilating function of the cell, in consequence, unsatisfied. The toxic effect of horse serum would in probability be due to such normal constituents as globulins and the great number of such elements concerned in the intoxication would perhaps preclude the possibility of neutralizing it by means of a specific serum. In the offspring of refractory mothers enough anaphylactin could pass into the fetal circulation to sensitize, but not enough of the assimilable substances to satisfy the cells. Anaphylaxis is dependent on the presence of the free anaphylactin. When the increased assimilating power of the overtrained cells of the anaphylactized animal has been satisfied, the further addition of horse serum produces no further effect. It can be conceived as possible to introduce the toxic serum, *i.e.*, the assimilable substances, so gradually as to produce no symptoms; at least, it may be said that the reaction varies directly with the size of the dose and the intimacy of its administration, or in brief, the brusqueness with which the increased cell avidity is satisfied.

As may have been deduced from our observation of the refractory guinea-pigs and their eventual sensitivity, animals which have once suffered severe symptoms and recovered, if reinjected after a sufficient period, may be made to undergo again the typical serum intoxication. By a proper dosage the disease may be repeated at relatively short intervals and as frequently as desired. By killing recovered animals at varying periods, healing lesions, such as gastric ulcers, may be studied, and, by repeating the disease, chronic conditions can probably be produced. Our observations, however, on these chronic lesions have hitherto been incidental, and we wish merely to indicate the undoubted value of a study along these lines. From the results in Experiment 9 it is evident that the localization of hemorrhages may be more or less controlled if the reaction be made sufficiently violent. In this experiment it will be noticed that the lesions correspond to the blood supply utilized and the rapidity of death; in the case of rapid death (three to ten minutes) injections into the jugular vein give hemorrhages of lungs and heart, injections into the carotid artery produce the same lesions and also affect the brain; that is, the lesser circulation alone is reached by the toxic serum; if, however, death is delayed (G.P. No. 5) gastric hemorrhages may also be produced. Injections into the left ventricle of the heart would be of interest.

In conclusion, it is of importance to consider certain general relations which exist between the anaphylactic serum and the affected organism in instances of serum anaphylaxis. It has been shown by Rosenau and Anderson that sera of animals other than the horse have an anaphylactic power against the guinea-pig. Of the sera mentioned by these authors, at least dog, cattle, and sheep are hemolytic for guinea-pig cells. Horse serum is no exception to the rule. Rosenau and Anderson, through inadequacies of technic, were unable to demonstrate this hemolytic body in horse serum; its existence, however, has been assured by competent observers, has served as the basis of an extended study by one of us,[18] and may be regarded as an established fact.

It has further been shown that in processes closely allied if not identical with the instances of anaphylaxis which we have studied, there is a definite relation between hemolytic bodies and effects produced. Arthus[19] found that a second injection of horse serum subcutaneously into rabbits which had previously been given horse serum at some distant point, even intravenously, gave localized necrosis; horse serum is also hemolytic for rabbit corpuscles. H. Pfeiffer[20] found that the necrotic action of normal sera occurs only in case the sera are hemolytic for the injected animal in question. It may be that we shall eventually find some general rule as to the concurrence of demonstrable antagonistic bodies and anaphylaxis. It may here be mentioned that the serum of the rabbit-anti-horse mentioned as of high precipitating power also contained anaphylactin, as was shown in the usual manner by injecting a normal guinea-pig and subsequently demonstrating its sensitivity (control of normal rabbit serum). This shows still further the analogy between hemolysis and anaphylaxis.

If a sensitized guinea-pig is injected with a horse serum deprived of hemolytic immune body for guinea-pig corpuscles, no decrease in the toxicity of the serum can be demonstrated. The toxic principle, then, is not dependent on the presence of the hemolytic body in this instance.

Experiment 13. — Six cubic centimeters horse serum was placed in contact with the sediment of 5 cubic centimeters of well-washed guinea-pig blood for 18 hours at 0° C. (Treated serum.)

Sensitized pigs (.1 cubic centimeter horse serum eleven days previously) were injected:

G.P. No. 3, weight, 495 grams, given 5 cubic centimeters treated serum.

G.P. No. 4, weight, 405 grams, given 5 cubic centimeters horse serum.

Both had equally severe symptoms but recovered.

The treated serum was proved by test-tube experiments to contain no longer the hemolytic immune body present in the untreated serum. It was not possible to demonstrate that the red cells of sensitized pigs are more susceptible to hemolysis by horse serum than are the red cells of normal guinea-pigs.

CONCLUSIONS.

1. The well-known susceptibility to intoxication by horse serum, which is demonstrable in guinea-pigs previously injected with horse serum, is due to the non-neutralization and non-elimination by the animal body of a factor in the serum, for which we suggest the name ANAPHYLACTIN. The intoxication caused by the second injection depends upon factors of the serum other than anaphylactin. These factors correspond to constituents of the serum eliminable by the animal body. The reaction of intoxication would seem to be a cellular one, dependent upon a heightened power of assimilation on the part of cells which have been subjected to the anaphylactic substance over a definite period of incubation.

2. The tissues of guinea-pigs, examined during the anaphylactic phase, show no characteristic lesions. Striking multiple hemorrhages, for some reason hitherto undescribed, accompany the toxic phase. The hemorrhages are more frequent in the stomach, cecum, lungs, and heart than elsewhere.

Microscopic study demonstrates that the hemorrhages are largely associated with widespread fatty degeneration of the capillary endothelium. The heart muscle, the voluntary muscle, the peripheral nerves, and the gastric epithelium show striking focal fatty changes, which are independent of the vascular lesions.

The task of the anaphylactin is apparently so to prepare various cell structures that their contained fat is made to flow rapidly together upon exposure to the toxic agent. The rapidity of this degeneration is striking, though it presents histologically the features of so-called "chronic" degeneration.

POSTSCRIPTUM. — As the manuscript of this article was about to be handed to the printer, there came to our attention two articles, one by Besredka and Steinhardt[21] and one by Nicolle,[22] which still further indicate the interest which attaches to this problem. Besredka and Steinhardt have added very little to the knowledge of serum anaphylaxis in the guinea-pig beyond that which had already been given by the contributions of Otto, and Rosenau and Anderson. They also have failed to note the striking lesions in this disease and have been misled into regarding the refractory condition as a state of immunity. They bring out, however, by intracerebral injections, that the intimacy with which the serum comes in contact with the body cells affects the rapidity and fatality of the disease. Our intracarotid method of injections makes this point much more evident. Their supposition that anaphylaxis depends on a sensitization of the brain is doubtless right so far as it goes, but, as we have shown, sensitivity is evidenced in the somatic cells of all parts of the body and is not confined to any definite organ.

Nicolle's contribution, while not dealing directly with the disease as we have studied it, nevertheless gives indications that anaphylactin, the unneutralized substance of horse serum, accounts for the phenomenon of localized necrosis which has been described by Arthus. It is gratifying to us that the persistence of this foreign element in the animal body seems to be a phenomenon not restricted to the single case in which we have studied it, but of a more general applicability. It is, of course, our hope that we shall be able to correlate other instances of anaphylaxis with the explanation which holds for the special instance which we have studied.

[We wish to express our thanks to Drs. W. H. Park, J. J. Kinyoun, and A. P. Hitchens for their courtesy in furnishing us with horse serum.]

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DESCRIPTION OF PLATES.

PLATE XII.

(Plates XII., XIII., and XIV., Fig. 6. *Guinea-pig stomach.*)

FIG. 1. — x 30 ca. Zenker fixation. Sharply defined focal destructive hemorrhage at base of fold in gastric mucosa.

FIG. 2. — x 45 ca. Formaldehyde fixation — Marchi. Viewed from left to right: 1. Erosion involving muscularis. 2. Fold showing epithelial fat and injected subepithelial capillaries. 3. Area of necrosis with fat. 4. Fold showing epithelial fat. 5. Deep area of necrosis with fat (obliquely set). 6. Fold showing dense deposit of epithelial fat.

PLATE XIII.

FIG. 3. — x 30 ca. Formaldehyde fixation — Marchi. Extreme injection with small hemorrhages of subepithelial capillaries. Gastric epithelium outside zone of injection shows small collections of dots, here somewhat inconspicuous, but shown with higher powers in Figs. 4 and 5.

FIG. 4. — x 1000. Below, hemorrhage from subepithelial capillary. Clusters of fat droplets in outer cells of gastric epithelium.

FIG. 5. — x 1000. Clusters of fat droplets in cells of gastric epithelium. Fat droplets lining capillary endothelium below.

PLATE XIV.

FIG. 6. — x 500. Single large subepithelial capillary distended with blood and lined with fat droplets. Occasional droplets elsewhere.

FIG. 7 (*Guinea-pig liver*). — x 30 ca. Formaldehyde fixation — Marchi. Cluster of cells containing fat. These clusters are probably not differential for the serum disease, but are found with some frequency therein. The foci are of irregular distribution and bear no special relation to the vascular supply of the liver.

FIG. 8 (*Guinea-pig kidney*). — x 1000. Capillary of pyramid region, between walls of two collecting tubules. Tubule walls free of fat. Fat droplets in capillary walls. This lesion resembles the capillary fatty change found in numerous foci of the stomach. The renal lesion is as a rule found in the pyramids where the circulation is slow.

PLATE XV. (*Guinea-pig heart.*)

FIG. 9. — x 45. Formaldehyde fixation — Marchi. Numerous sharply defined foci of fatty change. The figure represents by no means the maximum of fatty change found in some cases, but brings out the focality of the lesion. The heart, like the other organs, is not attacked *en bloc.*

FIG. 10. — x 1000. Isolated heart fiber lesion. Numerous fat droplets or drops with tendency to arrangement in rows.

FIG. 11. — x 1000. Border of hemorrhage into heart muscle. Unlaked blood. Intense fatty change in heart fibers.

Plate XVI. (*Guinea-pig striped muscle*, formaldehyde fixation — Marchi.)

Fig. 12. — x 1000. Muscle fibers near edge of fascicle. Three types of fiber shown: 1. Normal fibers. 2. Fibers with heightened refractility. 3. Fibers with more or less numerous fat droplets, shown scattered at various intervals, because the fibers are cut in cross section.

Figs. 13 and 14. — x 1000. Muscle fibers in longitudinal section, showing fat droplets in rows.

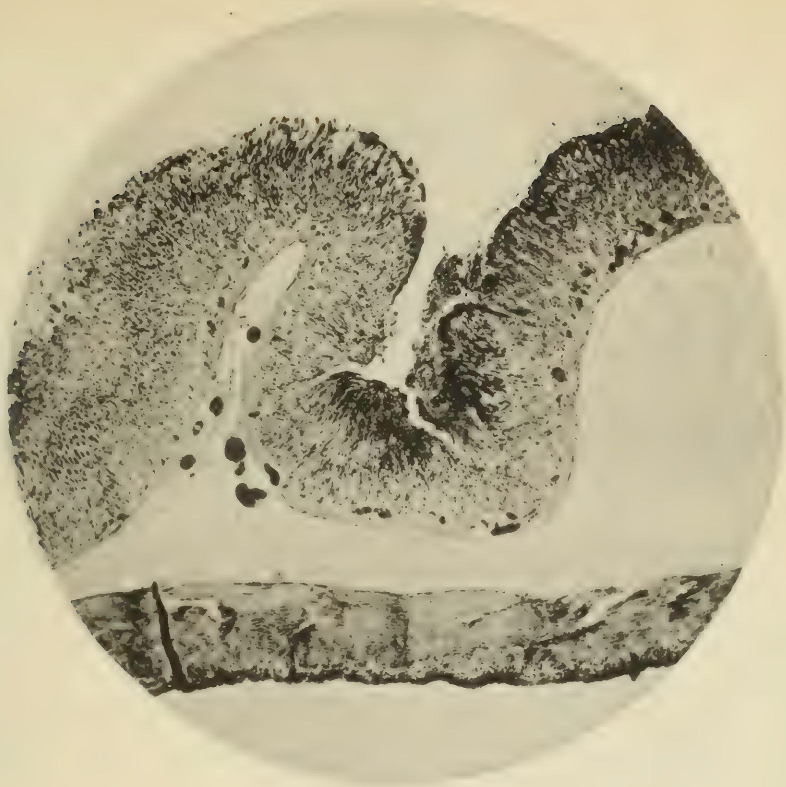
Plate XVII. (*Guinea-pig peripheral nerve*, formaldehyde fixation — Marchi.)

Fig. 15. — x 1000. Node of Ranvier. Swelling and blackening of myelin sheath for a brief interval on each side of the node. "Nodal change," early.

Fig. 16. — x 1000. Nodes of Ranvier. Swelling and formation of double-contoured bodies, blackened by the Marchi method, in myelin sheaths adjacent to nodes. "Nodal change."

Fig. 17. — x 1000. "Linear change." Collection of fat drops occupying site of former sheath."

The Journal of Medical Research, Vol. XVI., No. 2, May, 1907.



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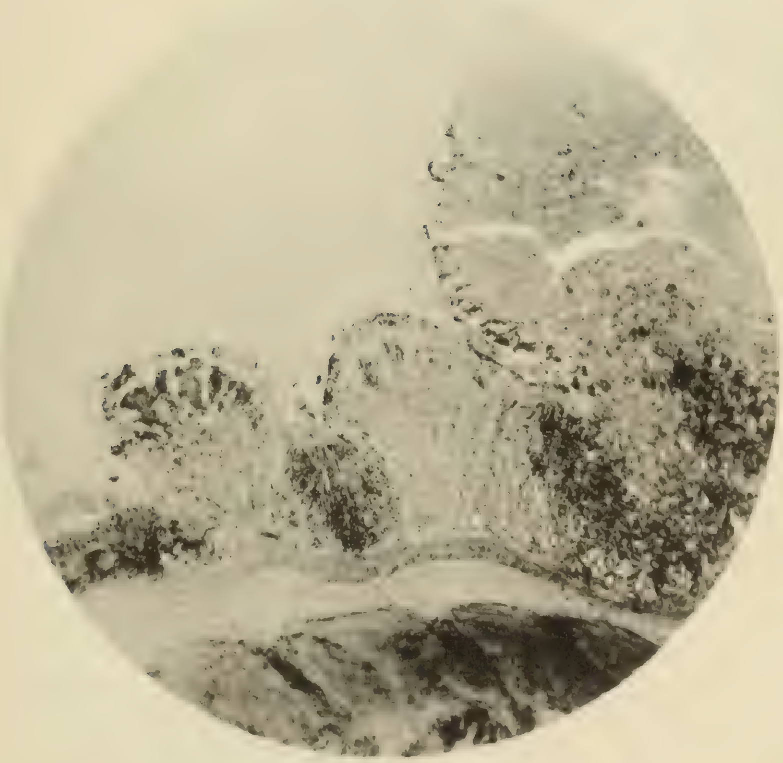

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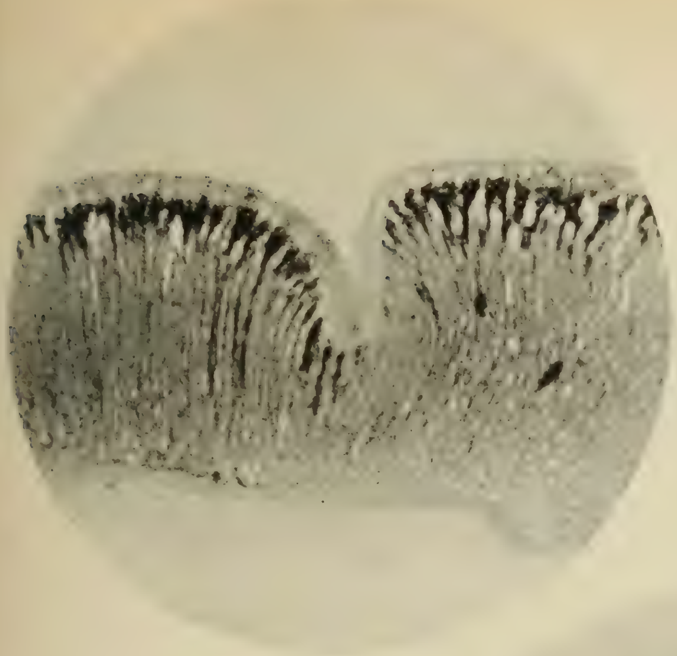

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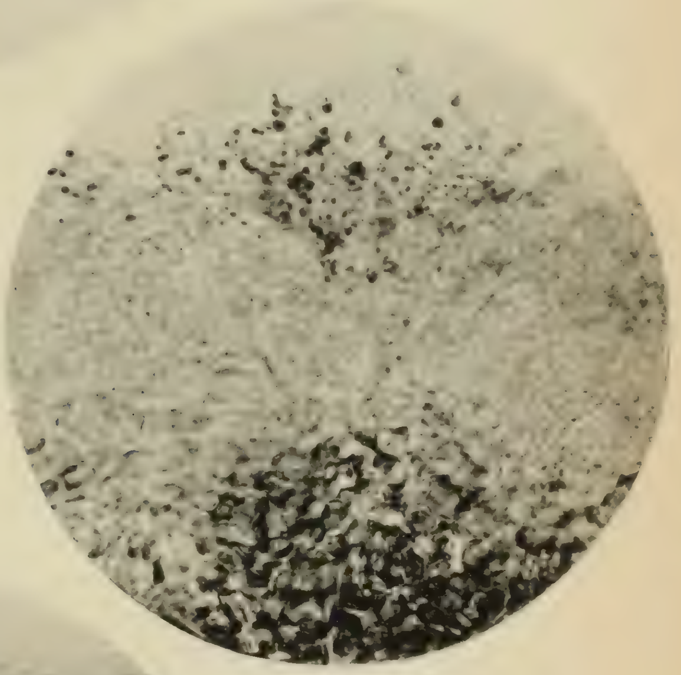

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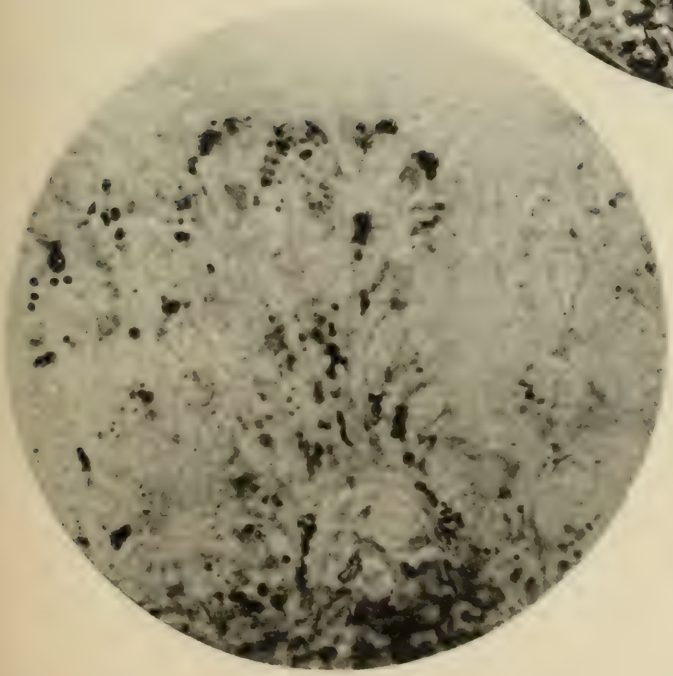

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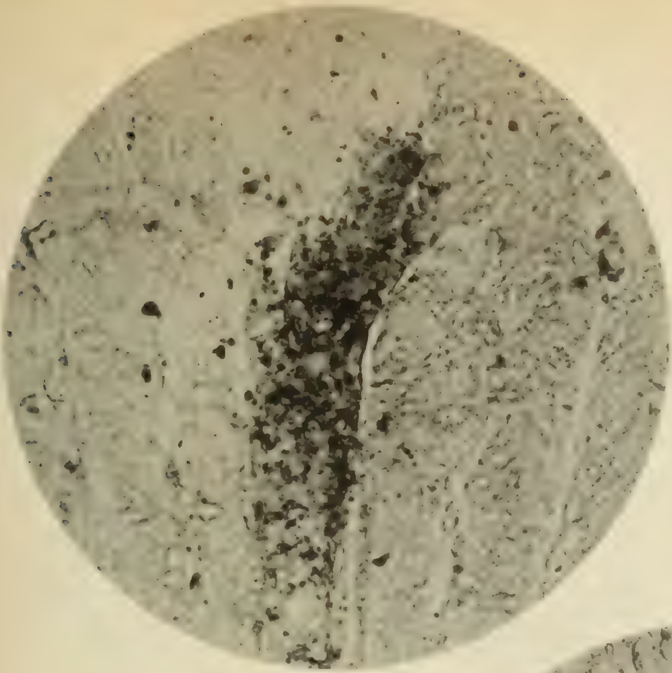

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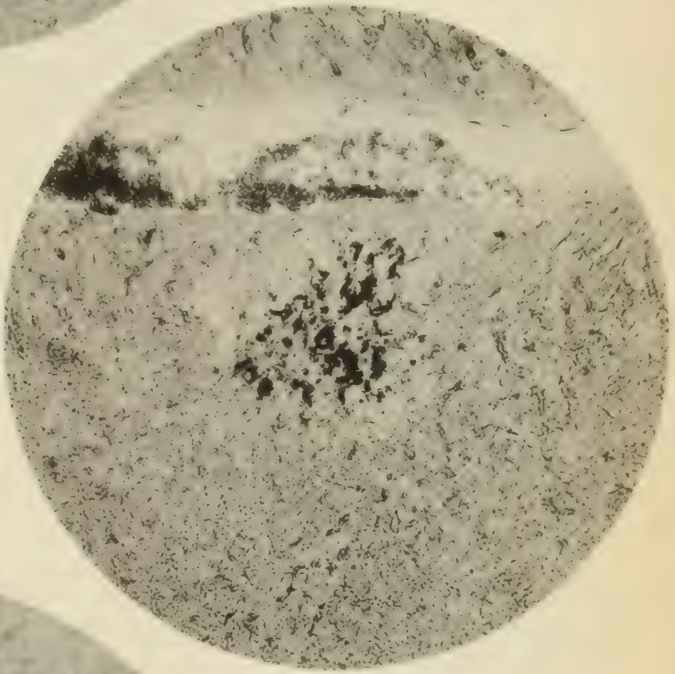

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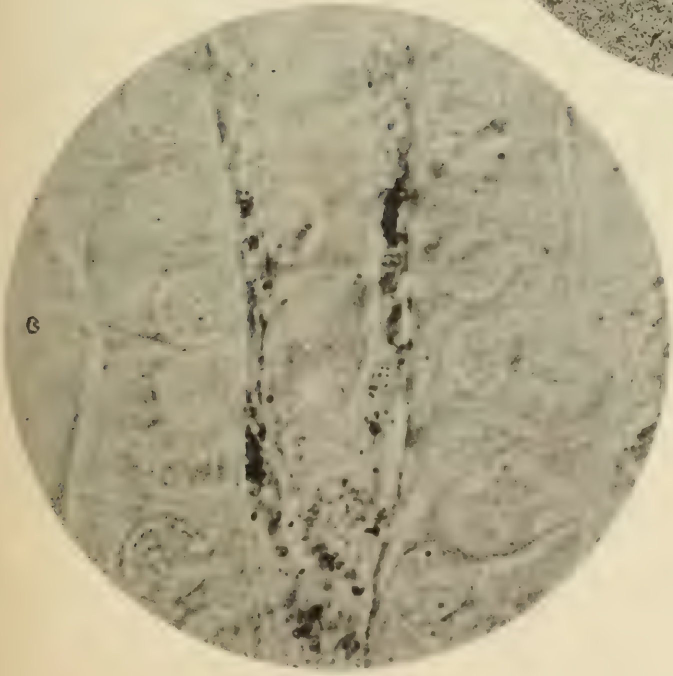

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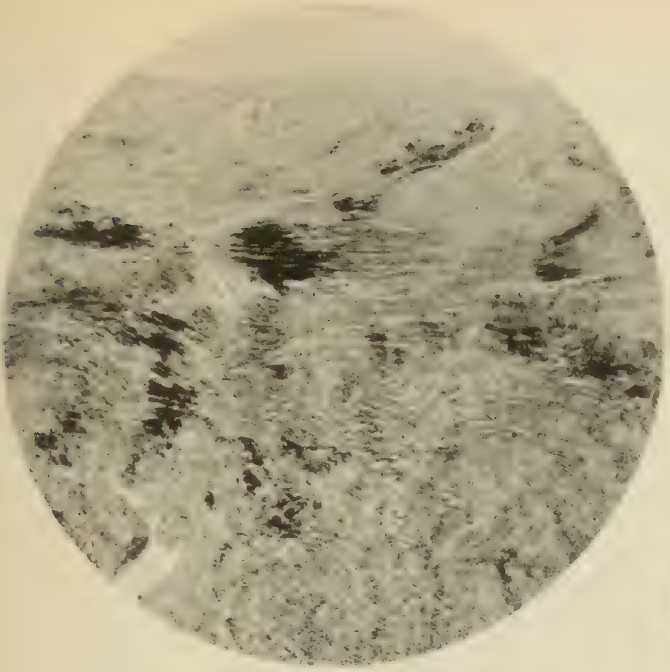

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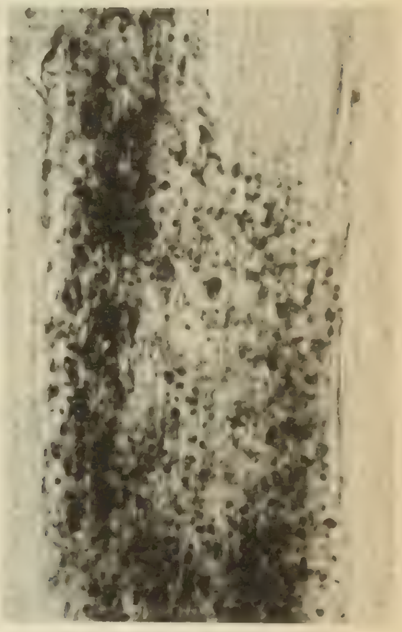

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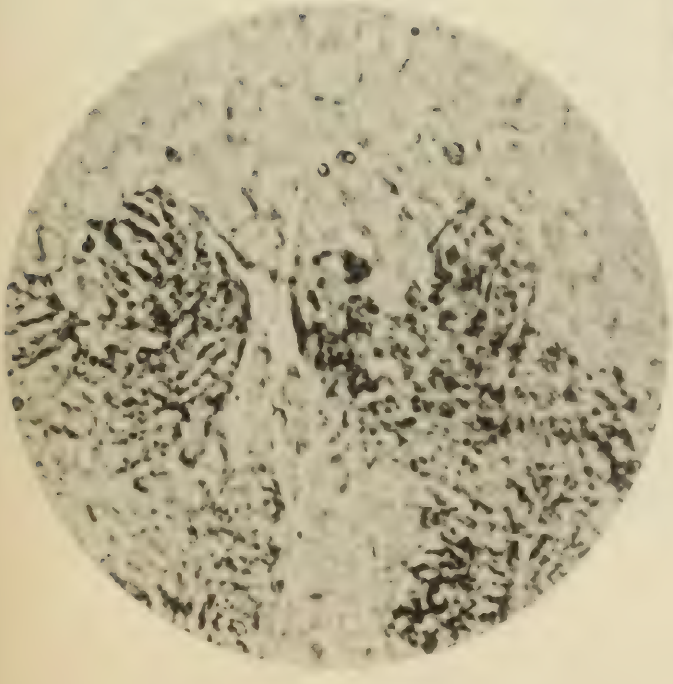

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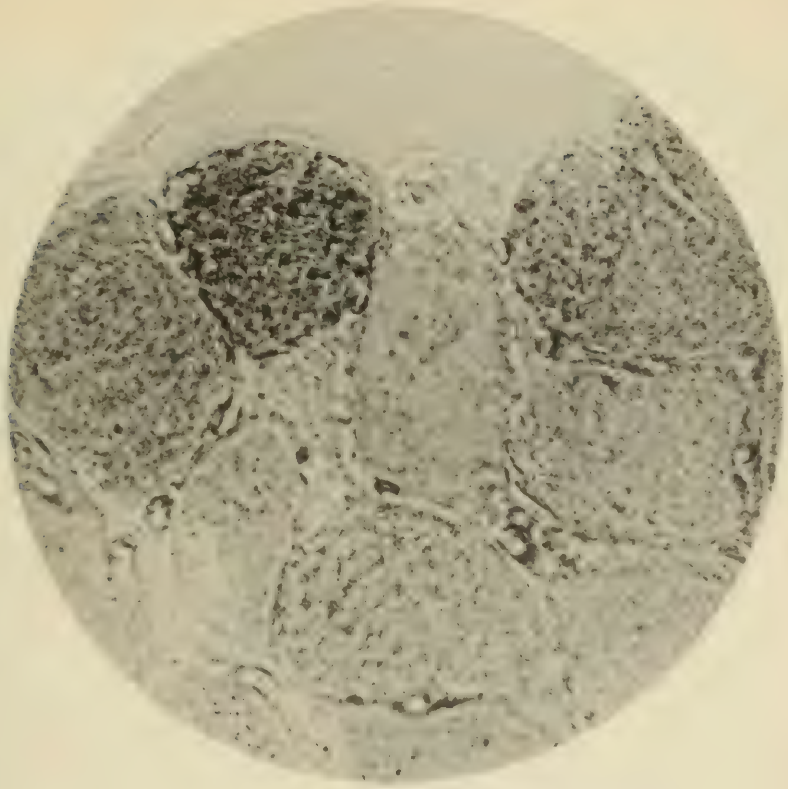
Gay and Southard Serum Anaphylaxis



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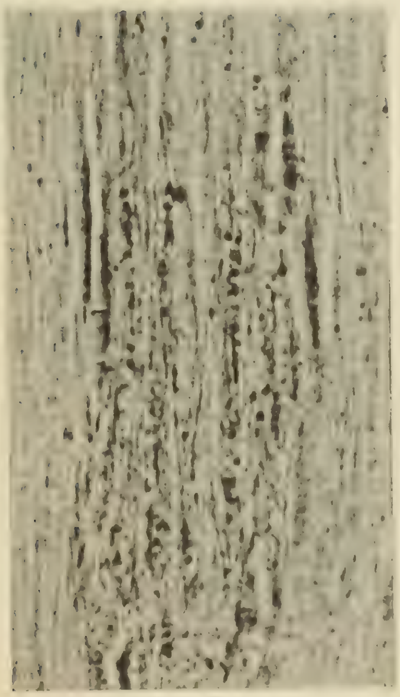

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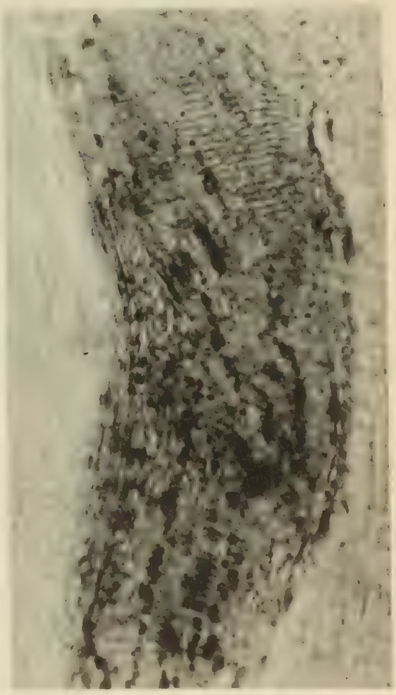

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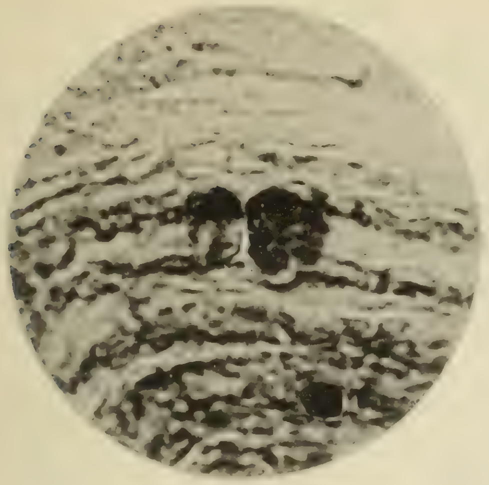

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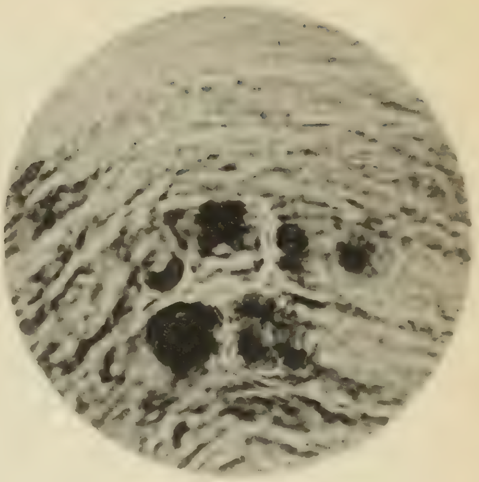

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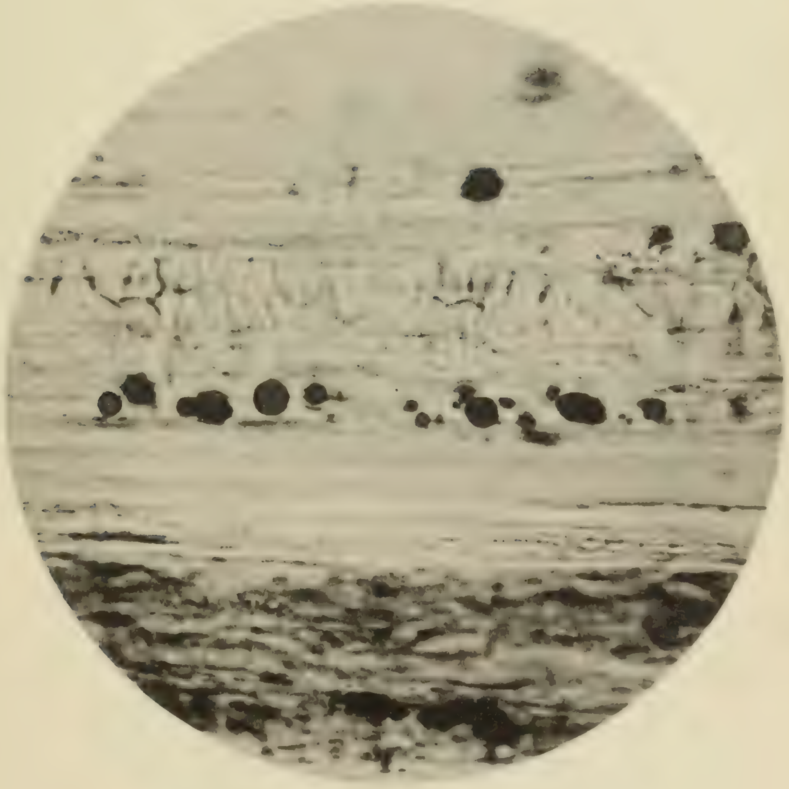

17

Diffuse and Focal Lesions in a Case of late Epilepsy.

DIFFUSE AND FOCAL LESIONS IN A CASE OF LATE EPILEPSY.

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The present case of late epilepsy yielded a multiplicity of lesions. Several of these lesions, as well as several combinations of them, might plausibly account for (or be ascribed to) the epilepsy.

The epilepsy was of fifteen years' standing, with death at the age of sixty-six. The most striking feature of the case was a focus of softening in the left cerebellar hemisphere. There were diffuse lesions of the rest of the nervous system, among them pigmentation with a tendency to affect certain cortical cell layers, perivascular gliosis notably of the spinal cord, and superficial focalglioses affecting the subpial layer in numerous regions of the cerebrum and the spinal cord. These latter focal glioses appear to have much in common with the "granules" of granular ependymitis, with which, in the hippocampal region of the present case, they are associated.

Workers in the field of epilepsy tend to exclude from study cases in which organic basis is assumed—such lesions being generally thought to be in the cerebral cortex. Experimental work has for years called attention to other possible sources of convulsions. The cerebellum should not be neglected in the study of the "Epileptogenous" areas. If the focal lesions of the cerebrum in such cases are regarded as causes or effects of epilepsy, then the occurrence of similar lesions in the spinal cord must also be taken into account.

CLINICAL HISTORY.

An Irish woman of sixty-three years was committed to the Danvers Insane Hospital, April 3, 1903, and died there August 31, 1906. On the night of admission she had a convulsive seizure and remained subject to such seizures at irregular intervals until the day of her death. She was subject to cardio-renal "ups and downs" and succumbed to an infection of the lower bowel.

On admission the patient showed general arteriosclerosis, (notably brachial and temporal), enlarged heart, varicose veins and ulcer of left leg, slight general anasarca, albuminuria and cylindruria. There were small pitted scars on the chest and a large scar at the angle of right scapula. Gait feeble, knee-jerks equal and diminished, extreme deafness. Memory impaired for remote as well as recent events. Memory defect appreciated by patient. Dull and sleepy.

The patient injured her forehead and face in her seizure the first night and had a slight fever thereafter. She grew better of this The albumin and cast disappeared from the urine within three weeks of entrance. She remained for the most part quiet and became tidy, was as a rule agreeable though variable in mood, and gradually became partially oriented for time, place, and for some persons.

A second seizure occurred early in May, 1903. July 22, she was irritable all day and had two general convulsions that night. She denied the convulsions next day. During the years following she would remain for the most part quiet and contented, gradually losing her orientation for time and becoming quite disoriented for place and person. Before and after her convulsions she was irritable. Later she would become confused after the seizures were over. She had occasional periods of weakness which confined her to bed. These periods followed the convulsions as a rule. At one time fever and signs in the lungs developed; but from these she made recovery.

The convulsions were general in character and are described, in 1906, as lasting ten to fifteen minutes, followed by stupor lasting several hours. Both arms and both legs moved. There was internal movement of the lower jaw; but no frothing at the mouth was observed. The eyes were closed. There was incontinence of urine and at times feces.

The terminal illness was ushered in by complaint of general weakness and several convulsions. Diarrhoea followed, and mucus and blood occurred in dejects on the fourth day. Death three days later. Convulsive movements of abdominal muscles an hour before death.*

FINDINGS AT AUTOPSY.

The autopsy was performed four hours post mortem. (E. E. S.) Head, cord and trunk were examined. A description of the head findings, together with an abstract of the other findings, follows:

(*I am indebted for the use of this history to Dr. W. P. Mitchell, Assistant Physician to the Danvers Insane Hospital.)

Head:—Hair, gray, fairly thick. Scalp, normal. Calvarium heavy and dense. Inner table of frontal bone raised in low smooth rounds, with which the dura mater has inseparably fused. Dura mater firmly attached to calvarium in bregmatic region and a long saggital suture. Dural sinuses contain suror clot. Arachnoidal villi in moderate amount. Pia mater of a normal appearance, contains little or no liquid over vertex. The basal cisternae contain considerable liquid. The basal vessels show a trifling amount of diffuse sclerotic thickening. Brain:—Weight, 1165 gms. Substance everywhere firmer than normal except over the right flank, which is softer than normal in the lower two-thirds of the central convolutions and the adjacent part of first temporal convolution. This soft part suggests plugging of associated vessels, but no vascular lesion was discovered on minute dissection. The section surfaces of the cerebral hemispheres are of a normal appearance, except that the white matter is more easily crushed under the soft place in the right hemisphere. The hippocampal gyri are not firmer than the rest of the brain. The brain was searched minutely for lesions which could be associated with epilepsy and sectioned throughout at intervals of 2mm. No lesion was found within the cranium except in the left hemisphere of the cerebellum. The substance of the left lobus clivi (lobus lunatus posterior) and the adjacent pia mater and opposite face of the postclival fissure (a thin strip of the left lobus cacuminis (lobus posterosuperior), contain, at a point 3 cm. to left of median line and 1.5 cm. anterior to posterior border of cerebellum, a focal lesion of lenticular shape, measuring 1x1x0.6 cm., with the flat faces tilting backward, upward, and slightly outward parallel with the plane of the postclival fissure. The lesion is cyst, a softening with coffee-jelly-like contents, shot through by vascular threads. There is no grossly evident zone of reaction about the lesion, which abuts directly upon the white matter of the lobus lunatus posterior and upon the main mass of cerebellar white matter, but has involved a part only of the cortex of the postero-superior lobe.

ANATOMICAL FINDINGS.

Acute ileitis, colitis, proctitis, with early serous exudate in peritoneum.

Acute vegetative aortic endocarditis.

Acute encephalitis (right central and first temporal gyri).

General arteriosclerosis (aortic, coronary, basal)

Mitral sclerosis.

Chronic fibrous myocarditis.

Brown atrophy of heart muscle.

Chronic diffuse nephritis with cysts.

Edema of ankles.

Slight emphysema of lungs.

Chronic gastritis.

Chronic adhesive pleuritis.

Chronic perityphlitis.

Chronic osteitis. (inner table of frontal bone).

Chronic external adhesive pachymeningitis.

Cerebral gliosis.

Small cyst of softening about left postclival fissure of cerebellum.

MICROSCOPIC FINDINGS.

Plates were made from the heart's blood, from the cerebrospinal fluid by way of the infundibulum, and from the left inferior frontal gyrus. The heart's blood showed staphylococcus pyogenes albus. The cerebrospinal fluid showed staphylococcus pyogenes aureus and a bacillus of the ambiguous group. The left inferior frontal gyrus was sterile. (Dr. F. P. Gay, Bacteriologist of the Danvers Insane Hospital).

The heart shows a moderate accumulation of perinuclear pigment in the great majority of fibers, a variable amount of fibrous thickening as a rule of interfascicular distribution, a moderate degree of sclerosis in some of the small coronary branches, ~~and~~ a trifling amount of subepicardial focal accumulation of mononuclear cells.

The lung shows, besides emphysema, a moderate number of phagocytic mononuclear cells in the alveoli. There is relatively more intense arteriosclerosis than in the heart. A mural thrombus with partial organization in one large artery failed to produce infarction.

The spleen shows chronic passive congestion of moderate degree. Extensive hyaline changes affect the walls of almost all the arteries. Small hemorrhages in pulp. Arteriosclerosis.

The liver shows a trivial amount of portal cirrhosis with an occasional focus of fibrosis and pigmented cells replacing some part of the lobule, as a rule nearer the portal tissue than the central veins. Slight chronic passive congestion.

The kidneys shows a variable amount of chronic interstitial overgrowth (in places extensive) a moderate degree of arteriosclerosis, and very numerous casts in the tubules.

The thyroid shows moderate arteriosclerosis and in places a voluminous accumulation of mononuclear cells about colloid, containing tubules. The majority of acini are free from these cells.

The pituitary body shows in the glandular part an unusual amount of colloid and a high proportion of eosinophile gland cells. One focus of maximal eosinophilia measures 2 mm. in diameter and lies about 2 mm. from the junction of the two portions.

The nerve cells of the gasserian ganglia are often pigmented. The pigment is often adjacent to the nuclei, but is sometimes found in the more usual peripheral site.

The spinal cord shows a heavy neuroglia framework throughout, as demonstrated by Mallory's phosphotungstic acid and hematein method after Zenker's fixation. The framework is particularly heavy in the subpial region of the posterior columns and in the vascular processes setting in therefrom. The subpial gliosis is best marked in sections taken from the lumbar region, where processes of glia make out in small promontories into the pia mater overlying the lateral columns. The interior of the cord shows the most marked fibrillar overgrowth about the central canal and along the edges of the gray matter adjacent to the posterior columns. The gliosis about the small vessels of the posterior columns is striking. The perivascular gliosis is best marked in the middle portions of the columns of Goll in the thoracic cord.

Axonal reactions cannot be demonstrated in the nerve cells of three segments of the spinal cord fixed in alcohol and stained by Nissl's method. The cells contain large pigment collections of the usual peripheral unifocal character. The cells of Clarke's column fail to show acute changes. Benda's neuroglia stain demonstrates a large number of corpora amylacea. The Weigert method for myelin sheaths and the Marchi method for fatty degeneration were used in numerous segments of the spinal cord. The dorsal columns of the cervical and, more markedly, of the thoracic portion of the cord show by Weigert's method a central faintly paler area of an oval shape symmetrically set along both sides of the dorsal septum. The Marchi method fails to show especial signs of degeneration in this area. Correlation of the Weigert findings with the data yielded by Mallory's phosphotungstic hematein method leads to the hypothesis that these paler areas are more probably due to an unusual strengthening of the perivascular neuroglia. There is perhaps a localized sheath and fiber degeneration corresponding therewith; but this cannot be demonstrated.

A similar hypothesis can be upheld for the character of the peripheral sclerosis so characteristically shown in phosphotungstic hematein preparations of the spinal cord, particularly in the lateral columns of the lumbar region: Neither Weigert nor Marchi preparations by themselves would with any certainty demonstrate this lesion of the subpial neuroglia.

An occasional ventral root bundle is completely paled out by the Weigert method. The best examples of this were found in the lumbo-sacral cord. The Marchi method in the sections studied failed to demonstrate examples of fresh destruction of isolated bundles, although there is considerable evidence of isolated single fibers impregnated by the Marchi method scattered throughout the cords and the roots.

Cortex Cerebri: In order to work upon a fair sample of cerebral material, sections were prepared from the superior frontal gyri, gyri recti, paracentral lobules, superior temporal gyri, occipital regions, and hippocampal gyri from symmetrical parts of the hemispheres, and stained by Nissl's methylene blue method and by Benda's method for neuroglia after alcohol fixation. These sections were supplemented by sections from hippocampal regions stained in several ways, in particular by Mallory's phosphotungstic acid hematein method, after fixation in Zenker's solution.

Several lesions of a minor character were made out. Of focal lesions may be obtained, first, a relative paucity or in places total absence of Betz cells in the left paracentral lobule, second, a sharply defined lane of destruction to all types of nerve cells cutting radially athwart one portion of the paracentral lobule, so as to efface all layers, in a streak 0 04 cm. wide at first, but flaring out wedgewise opposite the internal layer of large pyramidal cells, to a width of 0.08 cm. (remains of a miliary cortical infarct?)

There are several diffuse or widespread lesions in the cortex cerebri. (1) Pigmentation of the characteristic cells of the fusiform layer of the cortex is exhibited in all regions examined. The pigmentation is found also in the analogue of this layer in the hippocampal regions. (2) Pigmented neuróglia cells are found to some extent in all layers, though to a minor degree in the layers of stellate cells of different regions. There are numerous pigmented neuroglia cells in the middle of the fascia detata. (3) The nerve cell pigmentation, outside the wide spread pigmenting of the fusiform cell layer mentioned above, are a little variable in distribution. The external layer of large pyramidal cells tend to show nerve cell pigmentation more often than the other layers. Nevertheless the internal layer of large pyramidal cells, including the Betz cells, of the right paracentral lobule shows marked nerve cell pigmentation, as also the layer of small pyramidal cells in the right superior temporal gyrus. The occipital gyri, in the samples examined, show little nerve cell pigmentation, although they show considerable neuroglia cell pigmentation.

The nerve cells of the gyri recti and of the occipital regions stain less well than the cells everywhere, showing fewer Nissl bodies and yielding, in the left gyrus rectus, a number of examples of the axonal reaction of Nissl.

The most important lesion found in the hemispheres was a widespread focal superfical gliosis of the fibrillar type, shown in well-nigh every section examined for it. This focal gliosis was well-marked in both hippocampal gyri. In the hippocampal region, moreover, the essential resemblance of these foci to ependymal granules was strikingly brought out On following about the ependyma over the fascia dentata and the subpial region of the hippocampal gyrus, small lenticular glioses are found of approximately the same size and density in the two loci.

The cerebellum was sectioned in numerous places with the object of procuring a fair sample of conditions at large as well as those about the focal lesions.

The cerrebellar tissue at large shows a fair complement of Purkinje cells without notable increase of Bergmann fibers. The granule layer shows a moderate reduction of granule cells with persistence of the eosin structures of Denissenko. The neuroglia framework is delicate but above normal in amount. The increase appears related with a delicate perivascular increase of neuroglia which is best demonstrated in the white matter. The elastic stain demonstrates a general increase of elastic tissue which extends to the smaller vessels, especially well seen in the white core and in the granule layer.

A search was made for focalglioses of subpial distribution, since these might possibly be predicted from the occurrence of such very generally in the spinal cord and in the cortex cerebri. Superficial focal glioses were, however, absent in the parts of the cerebellum examined both by Benda's and by Mallory's method for neuroglia. The absence of corpora amylacea was also noteworthy.

The cystic lesion found at autopsy in the left cerebellar hemisphere resembled in all ways the classical ways of softening. The destruction was massive of all layers and the white core. The cyst liquor with phagocytic cells has in places tremendously dilated the clefts in the adventitia and a much strengthened perivascular neuroglia zone.

The layers differ in their reaction to the destructive lesion and present instructive appearances similar to those described by the writer in 1905.* Even where the fibrillar gliosis in the granular layer appears to be well-nigh maximal, a number of eosin structures of Denissenko persist, as described by the writer in 1906.†

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* "The Neuroglia Framework of the cerebellum in cases of Marginal Sclerosis." E. E. Southard, Journal of Medical Research, XIII, 5, August, 1905, p. 487.

Since the cerebral cortex showed so constantly in numerous examples the characteristic focal superficial fibrillar gliosis, it was thought possible the Weigert and Marchi sections might show evidences in a few places of acute lesions having the same focal superficial character. This was impossible to demonstrate with any certainty. Just as in the spinal cord and spinal nerve roots, so also in Marchi sections of the cortex isolated single fibers were found in various place swhich had been blackened by osmic acid. The regions examined of the present case gave rise to the suspicion that recent lesions could scarcely be excluded from the data in hand.

If, however, we hold ourselves strictly to the data of demonstration, it cannot be denied that these focal lesions may be gradual rather than acute in origin; it can certainly not yet be asserted that these characteristic foci are each one the product of (far less the cause of) an epileptic attack.

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† "Lesions of the Granular Layer of the Human Cerebellum." E. E. Southard. (To be presented.)

Although the cerebral cortex and the spinal cord are thus negative in respect to evidence of immediate nerve fiber injury as demonstrable by the Marchi method, yet it is not infrequent to find by the same method a certain variable amount of phagocytosis in the meninges and in the walls of the small cortical vessels. Clusters of fat-containing phagocytes are found notably in the walls of the small vessels supplying the hippocampal gyri. Perhaps not too much stress should be laid upon the occurrence of such cells in a brain over sixty years of age.

There seems at present no good method of estimating the degree of tissue waste which may be regarded as normal at any age. Moreover, if any importance is to be attached to these fat-containing cells in the cerebral meninges of this case, attention must also be given to the appearance of the same cells in the spinal meninges.

The findings are a bit more positive in Marchi sections of the focal cerebellar lesion, for, in the white centers of a few laminae in the neighborhood of the cyst, bundles of fibers are demonstrable which have been blackened by osmic acid. There bundles of blackened fibers, together with the occurrence of clusters of phagocytic cells containing fat in the walls of the cerebellar cyst, may be taken as evidence of progressive tissue injury in the cerebellar cortex.

REMARKS.

The present case demonstrates how many lesions of different types might be logically assumed to bear some relation to the epilepsy shown in life. It is not easy to pick out the actual relations from the logically possible relations. In the present case of late epilepsy, we may assume (1) that the lesions discovered have no relation with the epilepsy, or (2) that the lesions have a relation but an inessential or adventitious relation to the epilepsy, or (3) that the lesions do play an indispensable part in the epilepsy as (a) antecedents or (b) consequents.

It is doubtless impossible to say which of these assumptions is justifiable. This is equally true, in the total history of work of epileptogenesis, of the relations which have been assumed between epilepsy and various lesions discovered.

The history of work on epileptogenesis reveals a gradual evolution until it is now hazardous to talk of any demonstrable epileptogenic lesions save lesions of cerebral cortex. If epileptogenic agents back of the demonstrable lesions are invoked or epileptogenic agents which produce convulsion and leave no tissue sign are invoked, these agents are usually assumed to work primarily upon the cerebral cortex. Epilepsy has become a problem of cortical physiology, in which the hunt for lesions is incidental and indecisive though fruitful.

Fuller consideration of numerous points in the history of work on epilepsy will show that the disease is more than one of cerebral cortical physiology. Even if we confine ourselves to the nervous system in work on epileptogenesis, we shall find that lesions of very various site may be assured logically enough as related with epilepsy. Work on organic epilepsy is by no means univocal in pointing to the cerebral cortex as the sole epileptogenic zone or as an indispensable epileptogenic *point de passage*. In the literature perhaps the most positive plea for the wider search for epileptogenic centers is the neglected work of Brown-Sequard on epilepsy in guinea pigs subject to lesions of the spinal cord.

I have personally been fortunate enough to secure a number of cases in which it seemed wise not to neglect the cerebellum as in the epileptogenic center. The present case might be offered as such evidence. The strongest point I can make in this direction is that on minute search no other active destructive (in the sense of Marchi-reaction-producing) lesion of a focal character was found in the nervous system except a cyst of softening in the cerebellum. Elsewhere, both in the cerebral cortex and in the bulb and cord, there are found numerous subpial focal fibrillar141 glioses of a sharp and striking character. These foci of fibrillar glioses were attended by similar sharp and limited irregular foci of glioses along numerous vessels—a kind of miliary disseminated glioses of a perivascular distribution. Moreover, these miliary disseminated glioses of the subpial and perivascular regions were attended by certain granules in the ependyma of the ventricles, which granules were of approximately the same age and character as the miliary glioses. Neither these unusual miliary glioses of the cerebral cortex, nor the more banal neuroglia strengthenings of the spinal cord framework, nor the ependymal granules, were attended by active destruction of nerve tissue (in the sense of Marchi-reaction-producing focal destruction). Yet there was abundant evidence of a diffuse wear and tear in the nervous system in the form of numerous cells phagocytic for fat in many parts of the meninges and perivascular region of the cerebral cortex and spinal cord.

The relation of epilepsy to the cerebellar focus of active progressive destruction is of course in the last analysis doubtful. The relation to epilepsy of the miliary glioses of the cerebral cortex and the focal glia thickenings of spinal cord framework is possibly more doubtful. The characteristic hyperpigmentation of the nerve cells of the fusiform layer may be adventitious.

Investigation of numerous cases of late epilepsy on these lines is indicated.

NOTE ON CELL-FINDINGS IN SOFT BRAINS.

By E. E. SOUTHARD, M. D.,
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AND

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Reprinted from
AMERICAN JOURNAL OF INSANITY
Vol. LXIV, No. 2, October, 1907

NOTE ON CELL-FINDINGS IN SOFT BRAINS.[1]

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The present note calls attention to a point in pathological anatomy, viz., to the occasional occurrence at autopsy of brains and cords which are unduly soft to the feel, but have been subjected neither to edema nor to post mortem autolysis. Such reduction in consistence without increase of weight may be termed general encephalomalacia (myelomalacia). Some of the soft brains and cords show evidence of recent destruction of nerve fibers, demonstrable by familiar methods (Nissl's, Marchi's). The very diffuse malacia appears to be a phenomenon of terminal exhaustion and is perhaps related with such central neuritis (1) as may occur in Korsakoff's psychosis (2) and other conditions. The case of an epileptic dying at forty-two is given as paradigm of the condition.

Our attention was drawn to the condition in the course of work on accessible epilepsy tissues. Of course nowadays we very properly associate epilepsy rather with indurations of the brain than with encephalomalacia. As the appended case shows, however, the two conditions, focal sclerosis and general reduction in consistence without increase of weight, may be recognized together in the same subject It is even likely that focal glioses may stand out more prominently than usual in the soft brain and cord. Although recorded observations are not decisive on the point, it is not to be supposed that a large proportion of autopsied brains in epilepsy show malacia in this sense. We were surprised, however, to find that, out of a score of cases with soft brains (Danvers Insane Hospital series), a half-dozen proved (in the clinical records) epilepsy cases. But the histories failed to indicate that the encephalomalacia is directly related with epilepsy or with convulsions. Sometimes, as in the appended case, convulsions and other epileptic phenomena had ceased long before a terminal period of exhaustion, during which the lysis of nerve tissues had proceeded or begun. A review of the clinical histories in these cases pointed rather to a late, terminal, or agonal exhaustion than to any supposed convulsive constitution as the lytic agent. Some of the cases were febrile, others not, and some terminally febrile.

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[1] Read at the meeting of the American Association of Pathologists and Bacteriologists, Baltimore, 1906, and at the meeting of the New England Psychological Society at the Massachusetts Hospital for Epileptics, Palmer, 1906.

The general interpretation of such a finding is dubious. We are familiar with the general histolysis and swelling which follow shutting off the blood supply from a part of the brain (focal encephalomalacia with edema) and with the general softening down in situ of the brain after death (post mortem autolysis). The histology of these conditions differs from that of the general encephalomalacia under discussion. The soft brain (in the sense of this note) shows axonal reactions in nerve cells and Marchi degenerations in nerve fibers, which are of wide distribution and unequivocal as far as they go. The brain has been subjected not so much to a general histolysis as to a cytolysis or axonolysis. Although the effect produced is a general softening down of tissues, yet the lytic agent actually works differentially. This differential action is exemplified in the appended case, since the preserved nerve cells and nerve fibers within the sclerotic focus mentioned below show the same axonal reactions and Marchi degenerations as are shown by the cells and fibers of the brain at large. The neuroglial overgrowth is itself resistant to lysis but fails to protect the included nerve structures from lysis. This lytic change appears to be far more diffuse than any change which might underlie those changes in the second cortical layer of the brains of epileptics as first described by Bevan Lewis (3) or as described by Clark and Prout (4). It is to be observed, however, that Clark and Prout also mention chromatolysis in all types of cortical cell, most marked in the large pyramidal cells of the third layer. Bevan Lewis also notes the changes described by him as found to some degree in alcoholic brain-disease. The discovery of such changes both in and out of epilepsy makes clear how complex is the problem of the histology of epilepsy.

The practical recognition of this kind of brain and cord is important, because it would seem desirable for chemical pathology to begin upon work with cases showing such general disorder. Practically we are unable to draw many conclusions from the gross characters of brains examined very long post mortem. When the brain begins to stick to the knife on section, interpretation becomes difficult. Where post mortem changes can be excluded, there remain some sources of error. The chief source of error in the pathological diagnosis of soft brain would appear to be the occurrence of edema. The soft brain (in the sense of this note) is, however, not watery and fails to show the uneven cutting of gray and white matter, with tendency to bulging of the gray matter, which the edematous brain is apt to show. There seems also to be some evidence that a true terminal infectious encephalitis (of septicemic origin) is not infrequent; and we are not yet familiar with the possible effects of this upon nerve tissues. It is obvious that any or all of these softening agents may be combined. It is true also that a gliotic brain might not reveal to the fingers as much about injuries to the included fibers as would a brain of normal framework. It is possible that post mortem lysis proceeds with increased speed where a softening process has already begun ante mortem. The brain of encephalomalacia characteristically fails to show the increase of weight which is shown by edematous brains. Where brains are under weight at the outset, there is no good standard for determining the possible effect of the lytic changes on weight.

Following are the findings in a case chosen to illustrate the condition:

Clinical History.[2]

A. H., negress, age 42, was committed to the Danvers Insane Hospital July 14, 1902, discharged November 10, 1904, recommitted January 17, 1906, and discharged dead March 19, 1906, being under observation thus about thirty months.

Family History.—Incomplete; father died at 84; mother, of consumption at 54.

Personal History.—Woman of ordinary mental capacity. Characteristic epileptic attacks (unconsciousness, foaming at the mouth, biting of tongue, twitching) began eight or ten years before admission. The convulsions came every day or two for a month. She was "cured" of these at a hospital. Convulsions recurred three years before admission to Danvers, and came every month or two months. Before admission the patient had four fits and became thereafter dull and stupid, later disturbed and noisy. Both eyes were prominent, the left more than the right. Moderate external strabismus of left eye. Vision good. Was able to read. Ophthalmoscopic examination showed dilated and tortuous veins. Pupils equal, reacted to light. Knee-jerks equal, normal. Romberg's sign absent. The urine showed a trace of albumin.

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[2] Abstract made from the clinical records of Drs. H. A. Cotton and E. E. Bessey, assistant physicians to the Danvers Insane Hospital.

At admission: Inattentive, confused, talkative, hesitant in answering questions, pronouncing test phrases poorly and calculating poorly. Improvement for two weeks. July 31, three convulsions, followed by resistivism, confusion, vertigo, more unsteady gait, and headache. Cleared up in a few weeks and became an efficient ward helper, having three or four convulsions in a month, ushered in by a cry, followed by stupor for two hours or more. In February and March, 1903, severe headache with shooting pains in left temporal region, later over frontal region. Darting pains in right temporal region. Right pupil larger than left, very slow direct light reflex and slow consensual light reflex in right pupil. Left knee-jerk livelier than right. Clonus absent. Tongue slightly protruded to left.

April 6, convulsions, lasting two minutes. Head and eyes turned to left with twitching. Left hand held rigid. Right hand convulsed.

Discharged in 1904, improved. Orientation usually fair, memory good, insight into condition good, exophthalmos not so marked, considerable headache.

Readmitted January 17, 1906, weighing about twenty-five pounds less than at first admission and too weak to walk without support. External strabismus of left eye. Protrusion of both eyes, notably of left. Right pupil larger than left. Left knee-jerk brisker than right. Hebetude. Impairment of memory. Recognized persons, but failed to recall names. No spontaneous talk. On being aroused, said, "I don't know," or answered by "yes" or "no." Untidy. A few convulsions observed by nurse, lasting a few minutes, with eyes rolled upwards, head turned to the left, arms rigid, and a slight frothing at mouth.

Steady decline till death. Occasional slight convulsions. Expressions of fear or terrified looks. Confused, noisy, rolling about in bed. Conjunctivitis, and hypopyon of left eye. Stupor from which she can be aroused. Abdomen distended. Constipation. Difficulty in swallowing. Coma for twenty-four hours before death.

Anatomical Findings.

Autopsy eleven hours after death by E. E. Southard. Following are the findings in the head, together with the anatomical diagnoses:

Head.—Scalp edematous anteriorly. Calvarium thick, with little diploe. Dura adherent to calvarium in bregmatic region. Sinuses normal. Pia mater edematous, without notable thickenings. Brain weight, 1055 gms. Substance remarkably and evenly reduced in consistence in both white and gray matter. Olives and dentate nuclei as soft as normal cortex cerebri. The appearances resemble those of many days post mortem. The central convolution of the right hemisphere is much firmer than the surrounding convolutions. The right ascending frontal convolution is firm throughout the arm area and for a portion of the face and leg areas. The right ascending parietal convolution is equally firm for a like distance. The sclerosis is sharply marked off by sulci, by the postcentral sulci behind (so as to exclude the superior parietal and supramarginal regions) and by the anterior ramus of the inferior precentral sulcus and the superior frontal sulcus in front and above (so as to exclude the greater part of the middle frontal and the superior frontal gyri.) There is no demonstrable atrophy or chronic pial reaction in relation with the sclerosis. The white matter beneath presents no change except the universal reduction in consistence.

Cord.—Numerous calcified plaques in posterior lumbar pia.

Middle Ears.—Left middle ear contains semi-liquid pus. *Retinæ* removed from behind show left nerve-head reduced, about one-third in surface area. Vessels injected. *Marrow* of femur fatty.

ANATOMICAL DIAGNOSIS.

Encephalomalacia and myelomalacia.

Early bronchopneumonia, left lower lobe.

Sclerosis of middle two-thirds of right central convolutions and posterior part of right middle frontal convolution.

Atrophy of left optic nerve.

Conjunctivitis, keratitis, and hypopyon of left eye.

Left ophthalmoptosis.

General arteriosclerosis (aortic, coronary).

Slight mitral sclerosis.

Old infarct of kidney.

Chronic external adhesive pachymeningitis.

Chronic adhesive pleuritis.

Chronic focal adhesive pericarditis.

Mural and subperitoneal fibromyomata of uterus.

MICROSCOPIC FINDINGS.

Sections from seven regions in each hemisphere were examined by Nissl's method, together with several regions of the cerebellum and various levels of the spinal cord. Sections from adjacent regions were stained by Weigert's myelin sheath stain and impregnated by the method of Marchi for fat.

The details of the microscopic work are reserved for a later comparative study of this and similar cases. The finding common to all parts of the central nervous system examined was the axonal reaction of Nissl, with characteristic eccentricity of nucleus and solution of cytoplasmic bodies, in countless examples of those cell types in which this reaction can be made out. A closely similar change occurred in many of the Purkinje cells of the cerebellum; a large proportion of the horn cells of the spinal cord show the reaction in classical fashion. The Marchi reaction was appropriately diffuse. The number of fibers affected would suggest that far more cells of origin are affected than can be demonstrated as injured by the Nissl method.

REMARKS.

The anatomist is prone to neglect the general feel of the brain and cord at autopsy. He is familiar enough with focal alterations of consistence; thus, with foci of induration (scars, focal glioses) and with foci of subnormal consistence (focal encephalomalacia, focal encephalitis). A state of general induration is recognized as due to diffuse fibrillar gliosis. General reduction of consistence is least easy to interpret.

The plastic softness and swelling of edematous brains may be told from the diffluence of brains as autolyzed post mortem. We have here noted a condition of general encephalomalacia which we take to be of ante mortem origin, though doubtless it is speedily emphasized by post mortem changes.

The soft brains and soft cords of this group are not produced by vascular lesions and, unlike edematous organs, show no essential increase of volume or weight. This type of general encephalomalacia (myelomalacia) seems not unlike the state of the brain and cord after post mortem autolysis and is possibly due to a similar process.

Although the process has the appearance of a general histolysis, yet histological study shows that the lysis is essentially differential (diffuse axonal reactions in nerve cells and still more diffuse Marchi degenerations). Where, as in the illustrative case, a focal induration also occurs, the histolysis is readily seen to be differential because the nerve cells and fibers which still live in the sclerotic focus are subject to the same cytolyses (axonolyses) as are the cells and fibers of the brain at large. What the lytic agent is remains obscure.

General encephalomalacia (myelomalacia, neuromalacia?) is clinically related with a late, terminal, or agonal exhaustion and is sometimes seen following epilepsy as well as in other conditions.

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GLIOTIC CYST OF THE RIGHT SUPERIOR PARIETAL LOBULE.

By A. N. COLLINS and E. E. SOUTHARD.

(*From the Laboratories of the Boston City Hospital and the Danvers Insane Hospital.*)

Reprinted from
AMERICAN JOURNAL OF INSANITY
Vol. LXIV, No. 2, October, 1907

GLIOTIC CYST OF THE RIGHT SUPERIOR PARIETAL LOBULE.

BY A. N. COLLINS[1] AND E. E. SOUTHARD.

(From the Laboratories of the Boston City Hospital and the Danvers Insane Hospital.)

We wish to present a case of cerebral disorder in a young woman. The case ran a course of six years with general and focal symptoms and ended in death at the age of thirty-two. Two years after the onset of symptoms the skull was trephined over the right ascending parietal convolution at a point just anterior to the focal lesion found at autopsy four years later. This lesion was a cyst, 2.5 cm. in diameter, bounded internally by the ependyma of the lateral ventricle, externally by fibrous tissue continuous with the thickened and dimpled pia mater. On all other sides it was bounded by a zone of gliosis. The nature and origin of the cyst are in question. The condition may be classified perhaps as one of porencephaly. To avoid various connotations, we have called the condition gliotic cyst.

I. CLINICAL HISTORY.

An unmarried nurse of 28, after two years of severe parietal headaches accompanied by occasional vomiting and by impairment of vision, was admitted to the Boston City Hospital, January 1, 1894. Just before entrance she had suffered marked loss of power in left hand, arm, and leg, and the headaches had become intensified. Thermal, tactile, and muscular sense remained normal. The reflexes were unaltered.

On January 7 the right arm was somewhat improved, and she could walk with a hesitating gait. The headaches continued, and there was marked photophobia.

On March 25, after about eleven weeks of variable short periods of improvement and relapse, she was recommended to the surgical side for trephining. An aural examination before operation was reported negative. The skull was trephined by Dr.

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[1] Working in the fourth year elective in Neuropathology in the Harvard Medical School, 1905-1906.

E. H. Bradford just over the upper part of the fissure of Rolando. Some thinning of the skull at the point of trephine was noted. The dura bulged markedly. Pulsation was visible. The meninges were adherent to the inner table at one small spot. Nothing further was discovered.

The headaches returned on the third day after operation. On June 4, 1894, she was discharged only slightly relieved to the Convalescent Home where she remained until May 13, 1898, about four years. In the interim she had become completely blind. On May 13 she was admitted to the surgical side with a provisional diagnosis of general peritonitis. Operation the same day showed the entire length of the small intestine to be lifeless and black. The patient died in the afternoon.

II. FINDINGS AT AUTOPSY.

Autopsy the following day, by Dr. F. B. Mallory, showed thrombosis of the portal vein and its branches, infarction of the small intestine and multiple infarctions of the spleen. The brain showed, just back of the right postcentral convolution, a depressed area, greyish and rather fibrous in appearance. A frontal section through this point revealed an irregular stringy mass of rather dense fibrous looking tissue. This mass formed part of a wall of a cyst 2.5 cm. in diameter. The cyst reached to the right lateral ventricle and was only separated from the latter by the ependymal lining. The fibrous looking tissue projected in bands in all directions throughout the cyst and seemed to form a more or less intimate part of it. In other words the fibrous looking tissue did not form the wall of the cyst, but rather was included and extended in all directions therein, being limited peripherally by brain tissue only and not by a definite capsule or wall. No other lesions were found in the brain.

III. MICROSCOPIC EXAMINATION.

The microscopic examination was made largely to determine the cellular structure and pathogenesis of the cystic lesion in the right superior parietal lobule. It seemed possible to align this condition of gliotic cyst in the cerebral gray and white matter with the familiar condition of syringomyelia in the spinal cord. Syringomyelia in advanced cases can be faithfully described as a condition of gliotic cyst of the posterior horn and adjacent white matter. The present case showed a gliotic cyst of unknown duration (cerebral symptoms six years) involving gray and white matter of the cerebrum in an area which modern work has shown to be sensory in function.

Sections for microscopic study were taken to show tissue immediately surrounding the cyst, and the nature of its interior surface.

Four processes of staining were employed, *i. e.,* (1) Mallory's phosphotungstic acid-hematoxylin stain; (2) Mallory's anilin-blue stain for the intercellular connective-tissue fibrils; (3) alum-hematoxylin and eosin stain, and (4) Weigert's stain for myelin sheaths.

Microscopic examinations of these sections revealed the following: An absence of vascular lesions, an absence of phagocytic cells in the walls of blood vessels and of the cyst; some cellular and fibrillar gliosis in the subependymal region; an occasional tremendous spider-cell lying in the subependymal neuroglia; considerable fibrillar gliosis between the bundles of myelinated fibres; an absence of demonstrable neuroglia changes in the adjacent cortex as well as absence of subpial gliosis.

IV. REMARKS.

We have to deal in the present case with a condition of cyst with gliosis in the right superior parietal lobule. The cyst was 2.5 cm. in diameter and did not communicate with the lateral ventricle. The origin of the cyst comes in question.

We are able to do no more perhaps than enumerate possibilities.

Without reference to the subject's history, we might propose that this condition of gliotic cyst could be labelled anatomically as follows:

1. *Agenesia,* defining a condition in which the original tissue had never been deposited in embryonic life.

2. *Aplasia,* defining a condition in which the original elements laid down in this focus failed to develop for some reason.

3. *Necrosis* of focal character, defining a condition in which the necrotizing agent destroyed cells which had normally developed. Under this head might be considered:

(a) Infarction of embolic or thrombotic origin.

(b) Hemorrhage with absorption and incomplete repair.

(c) Abscess, turbercle, gumma, or other infective lesion, followed by absorption of disease products without adequate replacement with scar-tissue or gliosis.

(d) Echinococcus disease.

4. *Tumor* formation with cystic degeneration (cystic glioma or gliosis with cyst formation).

The history of the subject fails to support several of the possibilities mentioned and indeed seems inconsistent with a number of them. Perhaps the earliest symptoms were due more to heightened intracranial pressure than to the focal lesion. The greater emphasis at times of right parietal headache might be ascribed to the focal lesion. In any event the results of the focal lesion and the results of the consequent increase of intracranial pressure can hardly be separated clinically at this time.

The woman had been perfectly normal up to the onset of her disease six years before death. She had been a capable trained nurse. Clinically there could be no suspicion of maldevelopment, or of any form of bacterial or parasitic infection.

Disregarding the clinical data for the time being, we are in a position to exclude the likelihood of most of the possible conditions mentioned above. The absence of vessel lesions and of phagocytic cells is striking. The normal character of tissues a few millimeters distant from the gliotic wall of the cyst is suggestive of an acquired, rather than of a congenital, lesion.

We have thought it worth while to present the case as a phenomenon to be explained. No explanation seems so satisfactory as that of glioma with cystic degeneration. This diagnosis fails, however, to explain much, since the significance, both of glioma and of cystic degeneration, remains unclear. The best suggestion we can offer is that the condition is analogous to syringomyelia. Gliotic cysts of the cerebrum will be understood when syringomyelia is understood. Both conditions depend for their explanation upon the theory of neuroglia changes. Let the nerve tissues of a part of the superior parietal lobule in this case undergo a slow death like that in the tissues of the posterior horn of the spinal cord in a case of syringomyelia. Vascular lesions fail to ensue. The neuroglia attempts to fulfil the function usually attributed to it—replacement-gliosis. The attempt is a failure, as in the banal condition of cerebral infarction, and a condition grossly resembling a cyst of softening follows. Alterations in the amount of enclosed liquid ensue, just as in syringomyelia, and effect alterations of symptoms, complicated, however, to an extent not possible in syringomyelia, by heightened intracranial pressure.

Just as in syringomyelia, it is perhaps not possible to allege that the destruction of nerve elements in the area which afterwards becomes cystic is a primary or direct destruction of nerve elements. Is it possible that the gliosis is primary and not wholly a replacement-gliosis?

Further cases may determine whether there is a cerebral disease which proceeds on the lines of syringomyelia.

DESCRIPTION OF FIGURES.

FIG. 1.—Photograph of gliotic cyst, abutting on ventricle.

FIG. 2.—To show situation of cyst. Dotted lines are to represent dilatation of ventricles.

Sagittal section of right hemisphere taken 2.7 cm. from median line.

Dejerine, Anatomie des Centres Nerveux, 1895, Vol. I.

F_2, second frontal convolution. *FA*, ascending frontal convolution. *R*, fissure of Rolando. *PA*, ascending parietal convolution. O_2, second occipital convolution. *LN*, part of lenticular nucleus. *IC*, part of internal capsule. *V*, occipital horn of lateral ventricle.

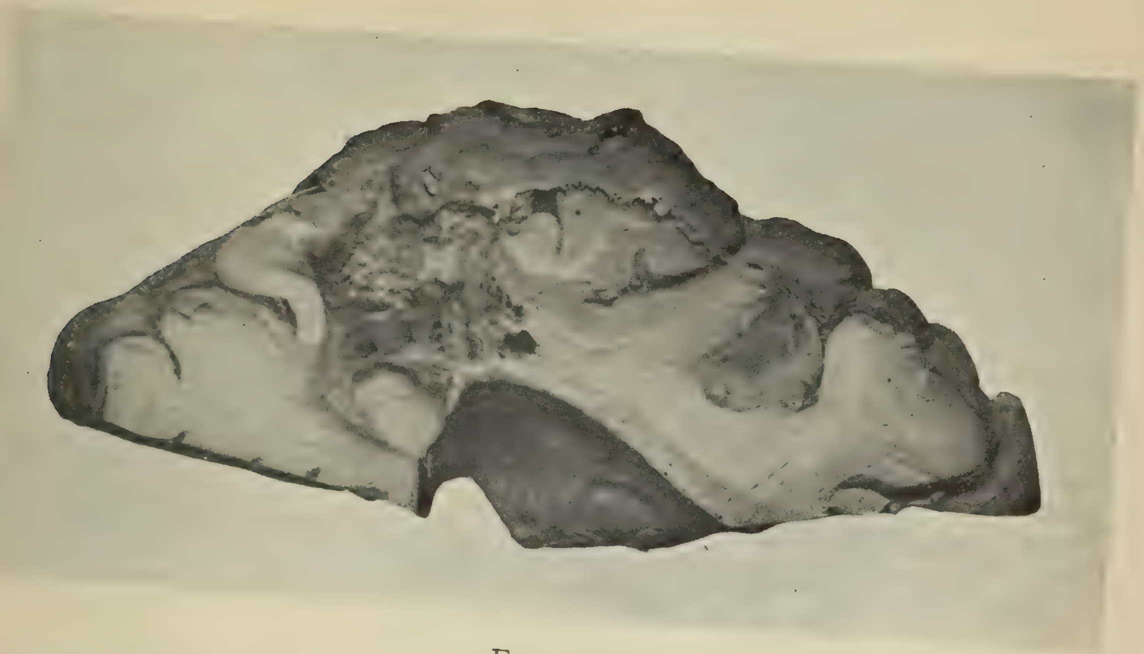

FIG. 1.

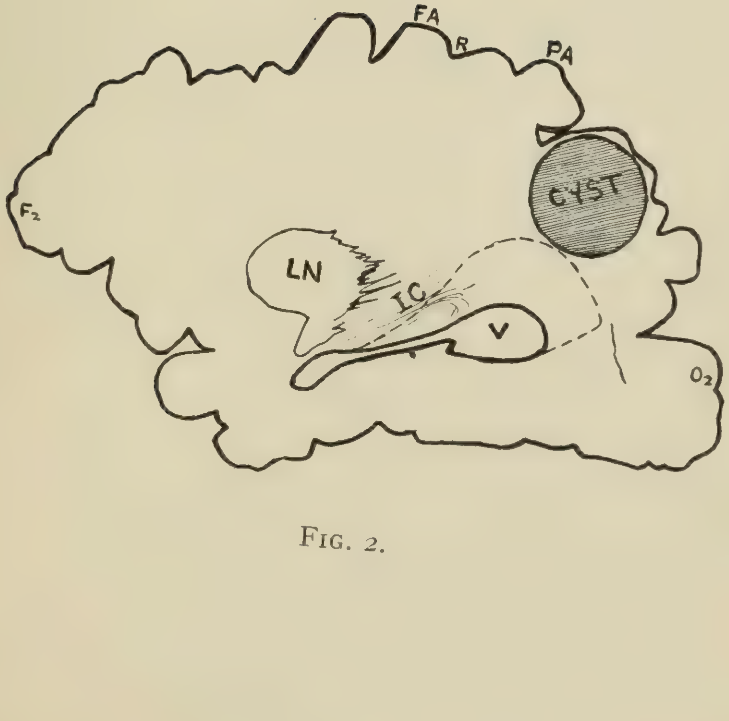

FIG. 2.

THE FUNCTION OF TONICITY IN HUMAN ISOHEMAGGLUTINATION

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Reprinted from
The Journal of Medical Research, Volume XVII., No. 3
(New Series, Vol. XII., No. 3), pp. 321–339, December, 1907

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THE FUNCTION OF TONICITY IN HUMAN ISOHEMAGGLUTINATION.* †

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The power of the blood serum of certain individuals to agglutinate the red blood cells of certain other individuals has interested clinical pathologists for some time. This interest has been sustained largely in the hope of finding a reaction of diagnostic importance in certain diseases, rather than from any appreciation of the causes which underlie the phenomenon. Whereas the earlier observers of human isohemagglutination asserted that isoagglutinins occurred only in the sera of pathological states, and was of specific and diagnostic importance, the later researches of Landsteiner[1] and others have shown conclusively that the sera of normal individuals quite as frequently clump the corpuscles of other normal or diseased persons.

In the course of the study of certain other properties of the blood serum in the insane my attention was frequently attracted to the isohemagglutination which occurred when the blood cells of some of these patients was mixed with the blood serum of others. Although the possibility of the existence of some specific relation as regards types of insanity naturally suggested itself, it was soon found that no such relation exists. Out of a tentative grouping of cases as regards agglutinability of corpuscles, or agglutinating power of certain sera, however, developed the study which serves as the basis of this communication.

As Landsteiner[2] was first to show, and as Hektoen[3] has since emphasized, the bloods of human beings may be definitely classed as regards isohemagglutination. It has been

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* This study was facilitated by a grant from the Proctor Fund of Harvard University.

† Read in abstract before the Society for Experimental Biology and Medicine, New York City, Oct. 16, 1907. Received for publication Oct. 24, 1907.

shown by these writers that three rather definite groups exist, in one of which nearly every human blood may be placed; apparent exceptions have been noted in a few instances by Hektoen. The groups have been classified by the latter writer as follows:

Group 1. — Contains those bloods the corpuscles of which are not agglutinated by the sera of Groups 2 and 3, and the sera of which agglutinate the corpuscles of Groups 2 and 3.

Group 2. — Bloods whose corpuscles are agglutinated by the sera of Groups 3 and 1, and whose sera agglutinate the corpuscles of Group 3.

Group 3. — Bloods whose corpuscles are agglutinated by the sera of Groups 2 and 1, and whose sera agglutinate the corpuscles of Group 2.

My observations lead me to concur entirely with Landsteiner as to the existence of three rather definite groups of human blood, considered from the standpoint of isoagglutination, although the line of experimentation which I have followed has not necessitated the study of any considerable number of individuals, such as might be necessary for an ultimate classification. I have been concerned entirely with an attempt to elucidate the conditions which underlie this form of agglutination.

The bloods studied were uniformly obtained by bleeding directly from the median, median cephalic, or median basilic vein of the arm, as seemed most convenient in the particular case. After scrubbing the arm with soap and water, five per cent carbolic, and then alcohol, a tourniquet was applied just above the elbow. A sterile, heavy, irido-platinum hollow needle measuring 1.5 millimeters in diameter and with a heavy butt, which may be grasped like a trochar, was then inserted directly into the engorged vein.* In this manner fifty cubic centimeters of blood may be obtained without any marked inconvenience to the patient. Blood for serum was allowed to clot in a sterile test-tube, and corpuscles were obtained by defibrinating a portion of the blood, caught in a shallow dish, by means of a clean glass rod; the serum, which subsequently rises on blood defibrinated in this manner, is not blood-stained, which shows that no mechanical hemolysis has been produced.

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* Dr. Crampton, formerly of the Pennsylvania Hospital, originated this needle in connection with a complete vacuum bleeding apparatus.

In testing the agglutinability of given corpuscles or the agglutinating power of a given serum an arbitrary dose of each has been used, namely, .5 of a cubic centimeter of a five per cent suspension of blood in .85 per cent NaCl solution, and .2 of a cubic centimeter of serum. The blood to be tested need not be washed in salt solution but may be made directly to a five per cent suspension. That the arbitrarily chosen dosage gives a correct indication of the relations of isoagglutination between the bloods, was repeatedly controlled by increasing the amount of serum in the case of absence of agglutination, and by decreasing it when agglutination occurred. When .2 of a cubic centimeter of serum gives no agglutination with a given blood, one cubic centimeter produces no more effect; when agglutination is positive in the chosen dosage it will be found frequently that the serum may be decreased to .02 of a cubic centimeter and yet give a positive reaction.

Human isohemagglutination is striking in its intensity and rapidity. In an instance where the reaction is markedly positive, small granular masses may be detected almost immediately after the serum is added to the corpuscles; these granules rapidly join to form a clot-like mass which settles to the bottom of the tube in from thirty to sixty minutes, leaving the supernatant fluid quite clear. These clots may be disintegrated by agitation so that the blood becomes apparently almost homogeneous, but they reform rapidly on being left standing. Repeated controls have convinced me that the presence and degree of hemagglutination may be detected quite as accurately macroscopically as microscopically. In the tables which follow the final results only are given, although tubes were inspected at room temperature at frequent intervals up to three to six hours and usually also the next day after conservation at 0° C.

The isohemagglutinating power of serum resists heating to

56° C. for thirty minutes, although the serum used in these experiments was freshly obtained and not heated. Isolysis, which occurred infrequently in the dosage used, was not particularly studied, and need not concern us except to note that lysis occurred much later than agglutination and gradually destroyed it.

It is evident that in any form of agglutination there are at least two factors to be considered, the serum which agglutinates, and the cells (bacterium or blood corpuscles) which are agglutinated. It would seem as if too much emphasis had been placed on the serum, owing largely to the assumption that agglutination is due to the existence of certain specific chemical bodies, "agglutinins," rather than caused by some variation of a physico-chemical nature. This assumption is due largely to the apparent proof of the presence in certain sera of several separate specific agglutinins. From the beginning of the study of human isohemagglutination I have been impressed by the agglutinability of a given blood, rather than the agglutinating power of a given serum, which impression has led to what would seem a profitable line of experimentation that will presently be detailed.

TABLE 1.*

Serum.	Agglutinable Corpuscles.						Nonagglutinable Corpuscles.										
	Group 1.				Group 2.												
	No. 17.	No. 26.	No. 30.	No. 33.	No. 23.	No. 25.	No. 34.	No. 35.	No. 32.	No. 13.	No. 14.	No. 15.	No. 16.	No. 18.	No. 21.	No. 24.	No. 27.
No. 17...	0	0	0	0	+	+	0	0	0	0	....	0	....	0	....	....	0
No. 26...	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0
No. 30...	0	0	0	0	+	+	0	0	0	....	....	....	....	0			
No. 33...	0	0	0	0	+	+	0	0	0								
No. 23...	+	+	+	+	0	0	0	0	0	0	....	....	....	0			
No. 25...	+	+	+	+	0	0	0	0		0							
No. 34...	+	+	+	+	+	+	0	0	0								
No. 35...	+	+	+	....	+	+	0	....	0								
No. 32...	+	+	+	....	+	....	....	....	0	....	....	....	....	0			
No. 13...	+	+	+	+	....	+	....	....	0	0	....	0	0	0			
No. 14...	+																
No. 15. .	+	+	+	+	....	+	0	0	0	0							

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* The observations in this table were obtained at different times, but may correctly be compared as conditions were found not to vary, in several cases in which three or four bleedings at intervals of from ten days to a month were made, over a period of two or three months.

TABLE I.— *Continued.*

	Agglutinable Corpuscles.						Nonagglutinable Corpuscles.										
	Group 1.				Group 2.												
Serum.	No. 17.	No. 26.	No. 30.	No. 33.	No. 23.	No. 25.	No. 34.	No. 35.	No. 32.	No. 13.	No. 14.	No. 15.	No. 16.	No. 18.	No. 21.	No. 24.	No. 27.
No. 16...	+	+	....	....	+	+	....	....	....	0	0	0	....	0	0	0	0
No. 18...	+	+	+	+	+	+	0	....	0	0	....	....	....	0			
No. 21...	+	+	+	+	....	+	0	....	0	0	...	....	....	....	0	0	0
No. 24...	+	+	+	+	+	+	0	0	0	0	0	0					
No. 27...	+	+	+	+	....	+	0	0	0	0	0	0					
No. 22...	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0
No. 19...	+	....	+	+	....	....	....	....	....	0							
No. 28...	+																
No. 29...	+																
No. 1...	+	....	....	....	....	....	....	....	....	0							
No. 2...	+	....	....	....	....	....	....	....	....	0							
No. 4...	+																
No. 3...	....	....	+	....	....	....	....	....	0								

In Table 1 are shown the cross agglutinations of a certain number of bloods which have been studied in considerable detail. It is seen that human corpuscles may be roughly divided into two general categories, those which are agglutinated by foreign human sera, and those which are not. The latter class, nonagglutinable corpuscles, predominate; in a total of twenty-four bloods studied, seventeen (or seventy-eight per cent) were nonagglutinable. The agglutinable class may further be divided into two general groups the members of which do not interagglutinate, but the sera of each one of which agglutinates the corpuscles of the other group as perfectly as do the sera of the nonagglutinable category. Of Group 1 of the agglutinable class (Blood Nos. 17, 26, 30, and 33 in the table) were found five in the twenty-four bloods studied. Of Group 2, agglutinable class, were found only two (Blood Nos. 23 and 25 in table). Between the two main categories certain general relations exist. The serum of a blood, the corpuscles of which are not agglutinated by any foreign human serum (Nos. 34, 35, 32, etc.), always agglutinates the corpuscles of any member of the two agglutinable groups.

It seemed in emphasizing the distinction between agglutinable corpuscles and nonagglutinable corpuscles that some other difference in the relative susceptibility of these categories of corpuscles might be found. Such indeed is the case if the relative resistance of such corpuscles to hypotonic salt solutions of different tonicities is tested.

The method which I have used for comparing the relative resistance of different human corpuscles to hypotonic salt solutions of different tonicities is essentially the one used by Theobald Smith[4] for red blood corpuscles of the horse, which in turn is a modification of Hamburger's method.[5] The bloods to be tested were defibrinated carefully with a clean glass rod so as to produce no artificial hemolysis. Salt solutions were prepared by dissolving NaCl (C. P. Eimer and Amend) in five hundred cubic centimeters of distilled water so as to make percentages ranging from .39 per cent to .6 per cent with variations of .03 per cent. The salt was heated to 170° C. for two hours before weighing. These solutions, although kept in tightly stoppered bottles, were not used over longer periods than from ten days to two weeks. In each experiment several bloods representing two or three of the groups already described were examined at a given time so that each experiment controlled itself as regards the relative resistance of the corpuscles studied; the results obtained at different times may also properly be compared. In every instance the bloods to be tested were used in from one to six hours after withdrawal. For each blood to be tested a series of tubes was prepared containing each five cubic centimeters of the salt solution of a different tonicity, and to each tube of a series was added one-tenth of a cubic centimeter of the defibrinated blood, measured in a carefully standardized pipette graduated to twentieths of a cubic centimeter. The same pipette was used to measure each blood in turn used in a given experiment. The resistance of the corpuscles was determined by the varying percentage of hemolysis present in the supernatant fluid of the different tubes after sedimentation, and this percentage of hemolysis was measured in the following manner: A standard tint of hemoglobin was made by laking four-tenths of a cubic centimeter of blood in twenty cubic centimeters of distilled water, which represented one hundred per cent of hemolysis, being in the same proportions as the prepared series; from this stock, one hundred per cent solution, tubes were made (each containing five cubic centimeters) by dilution with distilled water, to represent several percentages, usually eighty per cent, sixty per cent, forty per cent, twenty per cent, ten per cent, five per cent, and 2.5 per cent of the stock hemoglobin solution. On account of the obvious variations in the amount of hemoglobin present in different bloods it was found necessary to make a complete hemoglobin scale for each blood tested. After the tubes containing the mixtures of salt solution and blood had been made, they were allowed to stand at room temperature for from two to six hours when the sedimentation of the corpuscles became sufficient to allow the first reading; they were then shaken and placed at 0° C. until the next day when a second reading was made, which was found in most instances to be practically the same as the first reading. Very delicate differences in percentage can be detected in all the values below sixty or eighty per cent, above which it is difficult to determine with accuracy any slight variations.

In Table 2 is shown the comparative resistance of several human bloods chosen to represent the different isoagglutination groups (Table 1), as shown by the amount of hemolysis in hypotonic salt solutions. These bloods were tested at the same time and under as nearly as possible identical conditions, as has been described.

TABLE 2.

Tonicity of NaCl. Sol.	.39	.42	.45	.48	.51	.54	.57	.6	Category (Table 1).
	Percentage of Hemolysis.								
Blood No. 22...	100	90	75	50	25	5	0	0	Nonagglutinable blood.
" " 17...	90	65	25	15	5	2.5	0	0	Agglutinable, Group 1.
" " 26...	85	35	10	5	5	5	0	0	
" " 23...	65	25	5	5	5	2.5	0	0	Agglutinable, Group 2.
" " 25...	60	20	15	5	5	5	0	0	

In Tables 3, 4, and 5 are arranged the percentages of hemolysis of, (1) the same blood tested at different times, and (2) bloods grouped according to the agglutinating group to which they belong.

TABLE 3.

Nonagglutinable corpuscles.

Tonicity of NaCl. Sol.	.39	.42	.45	.48	.51	.54	.57	.6	Date Tested.
	Percentages of Hemolysis.								
Blood No. 22...	100	90	75	50	25	5	0	0	August 18, 1907.
" " 22...	100	40	15	5	2.5	2.5	0	0	August 26, 1907.
" " 18...	100	75	40	5	5	5	5	2.5	August 26, 1907.
" " 18...	100	100	60	35	10	2.5	0	0	September 24, 1907.
" " 34...	80(?)	80	35	15	10	2.5	2.5	0	August 21, 1907.
" " 35...	95	50	15	10	5	2.5	0	0	August 21, 1907.
" " 38...	95	35	10	10	2.5	0	0	0	September 2, 1907.

TABLE 4.

Agglutinable corpuscles, Group 1.

Tonicity of NaCl. Sol.	.39	.42	.45	.48	.51	.54	.57	.6	Date Tested.
	Percentage of Hemolysis.								
Blood No. 17...	90	65	25	15	5	2.5	0	0	August 18, 1907.
" " 17...	90	50	15	5	2.5	0	0	0	August 26, 1907.
" " 17...	60(?)	65	15	5	5	0	0	0	September 24, 1907.
" " 26...	85	35	10	5	5	5	0	0	August 18, 1907.
" " 26...	40	10	2.5	2.5	2.5	0	0	0	August 26, 1907.
" " 26...	85	35	5	5	5	5	0	0	September 24, 1907
" " 30...	70	70	10	5	2.5	0	0	0	August 21, 1907.
" " 33...	60	50	10	5	2.5	0	0	0	August 21, 1907.
" " 37...	70	45	2.5	5	0	0	0	0	September 2, 1907.

TABLE 5.

Agglutinable corpuscles, Group 2.

Tonicity of NaCl. Sol.	.39	.42	.45	.48	.51	.54	.57	.6	Date Tested.
	Percentage of Hemolysis.								
Blood No. 23...	65	25	5	5	5	2.5	0	0	August 18, 1907.
" " 23...	80	15	5	5	2.5	0	0	0	August 26, 1907.
" " 23...	50	40	10	5	0	0	0	0	September 24, 1907.
" " 25...	60	15	20	5	5	5	0	0	August 18, 1907.

Several facts are evident from a study of these tables:

1. It is clear that human corpuscles which are not agglutinated by foreign human sera are uniformly more susceptible to laking by salt solutions of low percentage than are corpuscles which are agglutinated by foreign iso sera.

2. It is evidenced (Table 2) that definite groups as regards resistance to salt solutions are present, which groups coincide with the groups classified according to agglutination.

3. The resistance of a given blood does not change apparently within a month or more and probably corresponds

to the relatively unchanging relations manifested in isoagglutination.

We should expect the tonicity of those corpuscles which are the more readily laked by salt solutions of low tonicity to be higher than the tonicity of those which are not so easily hemolyzed. On the generally accepted evidence that the tonicity of the red blood cell equals the tonicity of its surrounding serum, we should expect to find the tonicity of a serum belonging to Category 2 higher than sera of Category 1 (agglutinable corpuscles). Such indeed proves to be the case. When the tonicity of sera of the various groups was tested by adding increasing amounts of distilled water it was found that it is necessary to add more water to a serum of Category 2 to produce a mixture which completely lakes blood than to a serum of Category 1.

In the following experiment are tabulated the resultant grades of hemolysis of a tiny drop of blood from a finely drawn pipette when dropped directly into mixtures of distilled water and serum and immediately shaken. The grade of hemolysis was determined by the opacity of the fluid either by direct daylight, or more particularly by means of the sharpness or absence of definition of a cross marked on filter paper and held between a ground glass electric light bulb and the test-tube; very careful and repeated comparison of tubes tabulated as equal in grade of hemolysis was made. The mensurations of each serum and of the distilled water in a given experiment were made with the same standardized pipette calibrated to twentieths of a cubic centimeter. The hemolysis, while complete in a few minutes, was inspected at intervals over a period of several hours and the final result alone is given.

Table 6.

Tonicities of Sera.

(Tubes containing each one cubic centimeter of mixture.)

Serum.	·5 cc.	·45	·4	·35	Category.
Aq. dist.	·5 cc.	·55	.6	.65	
Serum No. 17.	Trace.	Slight.	Complete.	Complete	Agglutinable, Group 1.
" " 26.	No hemolysis.	Marked.	Complete.	Complete.	Agglutinable, Group 1.
" 23.	No hemolysis.	Marked.	Complete.	Complete.	Agglutinable, Group 2.
" " 18.	No hemolysis.	Slight.	Nearly complete.	Complete.	Nonagglutinable.
" " 22.	No hemolysis.	Trace.	Marked.	Complete.	Nonagglutinable.

The blood used in this experiment to detect grade of hemolysis was from Case No. 22. It is evident that Sera Nos. 18 and 22 are of a higher tonicity than the other sera belonging to the groups of agglutinable corpuscles.

It would be well to confirm these differences in molecular concentration by determining the differences in the freezing points of bloods belonging to the different groups which have been discussed. Hamburger[6] has shown, however, that differences in tonicity are far more delicately shown by the corpuscle resistance method than by estimation of the freezing point (Beckmann apparatus).

It is definite from these results that constant differences of molecular concentration accompany differences in human blood as exemplified in isoagglutination. It would not be safe, however, from such data to assert that these differences in tonicity are alone responsible for the phenomenon of agglutination. At first glance it might seem that hypertonicity of the foreign serum would explain why the sera of nonagglutinable corpuscles agglutinate the agglutinable corpuscles; this assumption would further explain why the sera of Group 1 (agglutinable) agglutinate the corpuscles of Group 2, whose corpuscles are of lower tonicity than those of Group 1; it would not, however, explain why Group 2 sera agglutinate the corpuscles of Group 1. Hitherto we have considered in speaking of tonicity one salt only, NaCl, but it is evident that whereas the relative resistance to hypotonic solutions of NaCl of two bloods may well represent the relative total molecular concentration of the blood of these two individuals, it gives no information of the relative concentration in different sera of different salts or colloids. It may well be that a serum hypertonic to another contains less KCl, for example, than the lower tonicity serum, and even if we were to assume that agglutination is due entirely to differences in tonicity, that it is due to physico-chemical differences and not to the presence of a specific chemical body (agglutinin), it would be necessary to study not only the simple salts of the blood but whatever colloids may be present. No attempt has been made to go farther into this aspect of the problem for the moment in the hope that similar differences in tonicity may underlie normal and artificial heterhemagglutination in animals and so afford a less difficult material for study.

The relative resistance of human corpuscles representative of the groups which have been considered was tested, however, with solutions of varying tonicity of $CaCl_2$ and it was found that the same relations hold as with NaCl solutions (see Table 7).

TABLE 7.

Resistance of corpuscles to $CaCl_2$ solutions.

(To each tube containing five cubic centimeters of each $CaCl_2$ solution was added .1 cubic centimeter defibrinated blood, the method following in detail that described for the test of resistance to NaCl solutions.)

Tonicity of $CaCl_2$ Sol.	.78	.81	.84	.87	.9	.93	.97
	Percentage of Hemolysis.						
Blood No. 17	50	40	20	5	2.5	2.5	5
" " 26	60	35	10	10	2.5	2.5	5
" " 23	10	10	2.5	5	2.5	0	2.5
" " 18	80	70	40	20	20	Trace.	2.5

The difference between the blood of Group 2 (No. 23) and the others is here very striking, as well as the differences between the categories, agglutinable and nonagglutinable.

It seems, moreover, evident that in isohemagglutination we have to deal with no such simple phenomenon as the increase in concentration of a single salt when we come to consider the well-known method of absorption which apparently has proved the existence of multiple specific agglutinins. As is the case with normal heterohemagglutinins (Bordet and Malkoff), normal isohemagglutinating sera may be shown by the absorption method to contain specific "agglutinins" for each group agglutinated.

Experiment 1. — 2.5 cubic centimeters of Serum No. 18 were added to the washed sediment of one cubic centimeter of Blood Nos. 17 (Group 1), 23 (Group 2), and 18 (control), respectively. After contact for three hours the mixtures were centrifugalized (Blood Nos. 17 and 23 were firmly agglutinated by the serum) and the supernatant fluids were tested as follows:

Sup. fluid A = Serum No. 18 in contact with Blood No. 17.
" " B = " " " " " " " 23.
" " C = " " " " " " " 18 (control).

Agglutinating power after absorption.

	Blood No. 17.	Blood No. 23.
Serum A, .25 cc....................	o	+
" B, " "	+	o
" C, " "	+	+

These absorbed sera may further be treated for four or more successive contacts with similar sediments of the same respective bloods without removing the agglutinating power for the other agglutinable blood.

As Landsteiner[7] has suggested in order to prove the specificity of each agglutinin in an agglutinating serum one should test, not with the fraction that is left in the absorbed serum, but with the substance bound to the cell. Such an experiment, in the case of human isohemagglutinins, does more to prove the strict specificity of each "bound agglutinin."

Experiment 2. — The sediments of A, B, and C in the last experiment were washed each in fifteen cubic centimeters of NaCl (.85 per cent) solution, centrifugalized, and two cubic centimeters of salt solution were added to each tube, and the mixtures heated to from 50–52° C. for one-half hour. They were then centrifugalized and the supernatant fluids, slightly blood tinged, were tested for agglutinins as follows:

1. Fluid from A corpuscles .6 cc. + Blood No. 17, .5 cc. 5% Aggl. = +
2. “ “ A “ “ “ + “ “ 23, “ “ “ “ = 0
3. “ “ B “ “ “ + “ “ 17, “ “ “ “ = 0
4. “ “ B “ “ “ + “ “ 23, “ “ “ “ = +
5. “ “ C “ “ “ + “ “ 17, “ “ “ “ = 0
6. “ “ C “ “ “ + “ “ 23, “ “ “ “ = 0

It is evident that the agglutinin bound to corpuscles No. 17 and liberated by heating to 50–52° C. is specific for No. 17 and will not agglutinate No. 23; conversely the agglutinin for No. 23 agglutinates only No. 23 corpuscles.

The specific agglutinating power in Serum No. 18 for Blood Nos. 17 and 23, respectively, is by no means inexplicable on the hypothesis that the isohemagglutination is due to differences in tonicity. A serum of the tonicity of No. 18 agglutinates bloods of the tonicity of Nos. 17 or 23; and serum of the tonicity of No. 17 agglutinates a blood of the tonicity of No. 23. We may well imagine when Serum No. 18 is saturated with Blood No. 17 that as a result of this agglutination the tonicity of the fluid becomes equal to that of No. 17 and, as such, can no longer agglutinate No. 17 but can agglutinate No. 23. It may be remarked that the determination of tonicity by the method used in Table 6 offers no definite proof that the tonicity of No. 17 is higher than that to No. 23, but the relative resistance of the corresponding corpuscles would seem to assure this difference. As a matter of fact it may be shown experimentally that *when an agglutinating serum is saturated with corpuscles which it agglutinates, the resultant, absorbed serum has changed in tonicity to equal that of the serum of the corpuscles agglutinated.*

Experiment 3.—Serum No. 32 agglutinates Blood No. 30. In conical tubes A and B were placed two cubic centimeters of defibrinated Blood Nos. 30 and 32, and after the addition of fifteen cubic centimeters NaCl solution (.85 per cent) the tubes were centrifugalized at a high speed (2,400 revolutions to the minute) for forty-five minutes. The supernatant fluids were removed with great care, leaving only the sediment of corpuscles. Mixtures were made as follows:

A. Sediment of 2 cc. Blood No. 30 + 3 cc. Serum No. 32.
B. " " " " " " 32 + 3 " " " 32.

Contact was allowed for an hour and a quarter at room temperature with frequent agitation, and the tubes were then thoroughly centrifugalized. It was shown that Supernatant A would no longer agglutinate Blood No. 30, whereas Supernatant B retained its agglutinating power undiminished.

The tonicities of fluids A and B, together with those of Sera Nos. 30 and 32, were then tested at the same time by the method described in Table 6 with the following result:

Table 8.

Tubes contain each one cubic centimeter of mixture.

Serum.	.5 cc.	.45	.4	.35	
Aq. dist.	.5 cc.	.55	.6	.65	
Serum No. 30..	No hemolysis.	No hemolysis.	Nearly complete.	Complete.	To each tube was added gtt. i of defibrinated Blood No. 32.
" " 32..	No hemolysis.	No hemolysis.	Slight.	Complete.	
" A.....	No hemolysis.	No hemolysis.	Nearly complete.	Complete.	
" B.....	No hemolysis.	No hemolysis.	Slight.	Complete.	

It is clear from such an experiment that Serum No. 32, which has been saturated by Blood No. 30 (A), has been lowered in tonicity to equal the tonicity of Blood No. 30.

If human isohemagglutination is due simply to increased concentration of one or several inorganic salts it should be possible to produce the phenomenon simply by increasing artificially one or more of these elements in isotonic solutions or in serum. No attempt has been made as yet to consider attentively this possibility, owing to conditions which have rendered access difficult to the material used for this study. Certain preliminary experiments may be mentioned as indicating the probability of artificially producing isohemagglutination by concentrating the salts. No marked differences in the form of agglutination caused by these solutions can be noted between corpuscles of the "nonagglutinable" and the "agglutinable" group, but such expressions do not, of course, indicate anything absolute beyond the relative conditions of isoagglutination in human sera. It is probable indeed that the solutions used vary markedly in tonicity from either of the bloods employed.

We may consider then the effect, for example, on corpuscles Nos. 30 and 32 produced by various solutions of $CaCl_2$ and NaCl. In this experiment .1 of a cubic centimeter of blood was added to five cubic centimeters of the solution indicated. Since the results were the same with both bloods, one description for each solution will suffice. Blood was shaken in the solution and allowed to remain at 0° C. over night. The first reading was then made and the tubes shaken and left at room temperature for four hours when they were again examined.

Experiment 4. — Solution 1. NaCl 1.6 per cent + $CaCl_2$ 1.8 per cent. A dense, coherent, viscous, clot-like mass at bottom of tube from which corpuscles are disintegrated only by vigorous shaking. This clot reforms and distinct hemolysis occurs.

Solution 2. NaCl 1.6 per cent. No cohesion; corpuscles diffused by gentle agitation. No hemolysis.

Solution 3. $CaCl_2$ 1.8 per cent. Slight coherent mass. No hemolysis.

Solution 4. NaCl 1.4 per cent + $CaCl_2$ 1.6 per cent. A dense, coherent, clot-like mass as in 1, breaks up more readily. Slight hemolysis after shaking.

Solution 5. NaCl 1.4 per cent. No cohesion. No hemolysis.

Solution 6. $CaCl_2$ 1.6 per cent. Questionable cohesion. No hemolysis.

Solution 7. NaCl .8 per cent + $CaCl_2$ .9 per cent. No cohesion. No hemolysis.

It cannot be said that the cohesion, or clot-like formation, in certain of these tubes is identical with isoagglutination by serum, but it has certainly many points of resemblance. As is seen from the results given, a solution which is isotonic in respect to both salts used (No. 7) produces no agglutinating effect, whereas an increase in the calcium salt alone produces slight agglutination, but the increase in both salts produce still more marked results. It will be of importance to attempt to form more characteristic agglutination by combinations of salts present in blood, including certain salts other than NaCl and $CaCl^2$.

CONCLUSIONS.

1. Human bloods may be separated into three rather definite groups as regards isoagglutination (Landsteiner, Hektoen).

2. Of these groups a distinction may be made between those bloods whose corpuscles are not agglutinated by any foreign human serum (Category 2) and whose sera agglutinate all members of the other category containing two groups, and bloods which are readily agglutinated by foreign human sera (Category 1, Groups 1 and 2).

3. Relative differences in the tonicity of human bloods, separated into these isoagglutinating groups, are constantly present. The bloods of Category 2 (nonagglutinable corpuscles, agglutinating sera) are constantly of higher total molecular concentration than bloods of Category 1 (Groups 1 and 2). Less notable differences of tonicity are present between members of Group 1 and Group 2 (Category 1).

4. A simple hypertonic solution of $CaCl_2$, but more particularly solutions hypertonic both in respect to NaCl

and $CaCl_2$, produces a cohesion of any human blood after several hours resembling specific isoagglutination.

5. The absorption of the agglutinating power of a given serum hypertonic to given corpuscles by those corpuscles, reduces the tonicity of the serum to that of the corpuscles agglutinated.

This would moreover account for the apparent demonstration of two separate agglutinins, one for each group agglutinated, since the tonicity, changed by agglutination, corresponds to the tonicity of the blood agglutinated, which blood in turn will also agglutinate a member of the other group.

6. There is strong evidence for the belief that isoagglutination of human blood may be due simply to physico-chemical variations of molecular concentration, and independent of the presence of any hypothetical new chemical complex (agglutinin).

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THE DETERMINATION OF THE ALEXIC ACTIVITY OF HUMAN BLOOD SERUM

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ALEXIC ACTIVITY OF THE BLOOD SERUM OF CADAVERS

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Reprinted from
The Journal of Medical Research, Volume XVII., No. 3
(New Series, Vol. XII., No. 3), pp. 341-359, and pp. 361-364, December, 1907

BOSTON
MASSACHUSETTS
U.S.A.

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It would seem evident that no single factor will account for the resistance of animals to infection; it is, however, by emphasis on different single factors that our knowledge of immunity has been advanced. From the present standpoint the blood is the body tissue most active in defence of the organism, which seems natural in view of its fluid nature and ubiquity. The observations of Fodor and of Nuttall showed that the fresh blood of various animals has the power of destroying bacteria, which power is lost on heating to 56° C. It was then showed by Buchner that blood serum, expressed by the contraction of the blood clot, has all the bactericidal properties of the whole blood, and Metchnikoff, on the other hand, demonstrated the ability of the leucocytes to engulf and destroy bacteria. From these fundamental observations have developed studies which have proved conclusively the importance in the animal defence both of blood cells and of the blood fluid. The enthusiasm of the advocates either of the humoral or the cellular theory of immunity has led to alternating periods of over-emphasis of the importance of one or the other factor, but the increasing data which have resulted from the two view-points are, in essentials, not antagonistic but reciprocal.

Buchner attributed the power of the blood serum to destroy bacteria to the presence of certain thermolabile,

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* This work was facilitated by a grant from the Proctor Fund of Harvard University. Received for publication Nov. 6, 1907.

ferment-like bodies to which he gave the name of "alexins" (Gr. ἀλέξειν = to ward off). It was later shown by Pfeiffer that, at least in the case of increased artificial immunity, destruction of organisms was due to the presence of new formed substances in the serum of the immunized animals. This author found that when cholera vibrios were injected into the peritoneal cavity of guinea-pigs which had been immunized by vaccination with killed cholera cultures, the organisms rapidly underwent granular disintegration, and the animals survived; and later he showed that this same phenomenon of bacteriolysis (Pfeiffer's phenomenon) took place in the peritoneal cavity of normal guinea-pigs, provided the vibrios had previously been treated with the serum of a specifically immunized animal. Controls in the abdominal cavity of normal guinea-pigs, with or without the addition of normal guinea-pig serum, gave no destruction of the spirillum and the animal died of a characteristic infection. Metchnikoff showed that Pfeiffer's phenomenon could occur in the test-tube when vibrios were mixed with immune serum if fresh peritoneal exudate was added. Bordet then found that a clumping of the cholera organisms, followed by their destruction, would take place in vitro on the addition of *fresh* immune serum alone. With serum which had stood at room temperature for some days or which had been heated to 55° C. for twenty minutes, the power of bacteriolysis was lost; and he found that the addition of fresh serum from a normal animal, in itself harmless to the organisms, would restore the bacteriolytic power to the heated or aged immune serum. From these data it was easy to conclude that in the case of bacteriolysis by specific immune serum the destruction of the organisms depends on two factors: first, a specific body acquired by immunization which is not destroyed by heating to 55° C., and second, a substance present in normal sera destroyed by heat or by standing at ordinary temperatures.

To the first of these substances Bordet gave the name of "substance sensibilisatrice" or sensitizing substance, and for the second substance, which, in reality corresponds to the destructive factor in Buchner's serum, he retained the name of "alexin." It has since been proved that the destruction of bacteria by normal sera is likewise dependent on the presence of the same two substances, an immune body (Bordet's substance sensibilisatrice) and the alexin; the normal immune body, however, in normal sera is much less potent than the artificial immune body present in immunized animals.

The studies of artificial hemolysis begun by Bordet in 1898, and continued by him and by Ehrlich and Morgenroth, have added much information as to the method of interaction of the immune body and alexin. Bordet found that if an animal of species "A" is immunized with red blood cells of an animal of species "B," on which cells under normal conditions the serum of "A" has no effect, that the serum of "A" acquires the property of hemolyzing or laking the specific corpuscles with which the animal has been inoculated. This artificial hemolysis is likewise due to the interaction of a specific, relatively thermostabile immune body, and the normal thermolabile alexin, and the process of foreign blood destruction is in essentials similar to the destruction of bacteria. Normal hemolytic sera are likewise dependent on the interaction of the two substances.

The further study of hemolysis by Bordet and by Ehrlich and his followers has contributed much information as to the mechanism of animal resistance. Although differences of opinion as to the method of action of immune body and alexin have at times seemed paramount between the French and the German scientists, the stimulus of rival conceptions has elicited much of theoretical and practical interest. It is not pertinent to the present discussion to analyze the accepted experimental evidence on which Bordet has built up a physico-chemical theory of immunity, nor the somewhat more abundant though no more ultimate data on which Ehrlich has constructed a purely chemical hypothesis; reference will be made in proper place to such differences of opinion as affect or are affected by the experimental evidence which we wish to present.

On the basis of a somewhat different conception of the interaction of the immune body and alexin Ehrlich has called the former, the "substance sensibilisatrice" of Bordet, the "amboceptor," and the alexin so called by Buchner and by Bordet, the "complement," or more exactly the "complements," since he conceives of the reactivation by fresh normal serum as due to a multiplicity of specific bodies each fitted to reactivate a single specific amboceptor. Apart from any personal prejudice as to the ultimate accuracy of the theory of either school, we prefer to use the terms "immune body" and "alexin" as non-committal.

On the data that have been mentioned the consensus of opinion attributes the variation of resistance in normal and diseased individuals, at least so far as such resistance is evidenced in the blood serum, to fluctuations in that factor which is the essential destructive agent for invading organisms, namely, the alexin. The immune body being formed by reaction to a specific substance suffers relatively little change under normal conditions or, indeed, under any diseased condition other than the one caused by the antigen to which it is the reaction product.

The origin of the alexin of blood serum is at least in large part from the leucocytes, but in just what proportion it occurs in normal plasma and in what proportion the alexin in serum is an artificial product of clotting is as yet uncertain. At least its proportion in serum must serve as an index of the resistance of the blood as a whole, whether intra or extracellular. Since the experiments on which the humoral theory is founded many attempts have been made to determine the fluctuations of the alexin in relation to disease.

It was experimentally shown by Szekely and Szana[1] as early as 1892 that the blood of rabbits infected with anthrax lost the power, just before death, to destroy these organisms, observations which were confirmed and amplified by Wilde.[2] Sweet[3] has shown that experimental diabetes in rabbits, caused by removal of the pancreas, decreases the alexic power of the blood.

Longcope,[4] in a study of the alexic activity of the human blood, demonstrated a decrease in certain chronic diseases which are particularly prone to terminal infections. Loewenstein[5] found a similar decrease of alexin in human diabetics, and in certain infectious diseases the power of the patients' blood was claimed to show a decreased power to destroy the causal organism of the disease. Perkins and Pay[6] and Thompson[7] showed fluctuations in the alexic content in variola, fluctuations which had apparently some relation to prognosis in the disease.

The observations on the alexic content in human beings that have been referred to, although undoubtedly demonstrating variations from the condition in normal human beings, are open to serious objections on account of the methods employed, and it is for the purpose of offering a new method, superior, we believe, in all respects to those in vogue, that this communication is made. Basing their technic largely on the supposition of the Ehrlich hypothesis of immunity, which maintains that the bacteriolytic and the hemolytic alexins (complements) are separate, these authors have attempted to determine the alexic power of the human serum to be tested by their power to reactivate heated normal human serum which contains a normal immune body for certain bacteria.

In the first place a logical interpretation of the Ehrlich theory would necessitate the determination not of the "complement" content for the destruction of any indefinite bacterium, for example the B. typhosus, but the determination of the content for the specific organism against which the individual is struggling, or to which he will eventually succumb, since not only are the bacteriolytic "complements" supposed to be separate from the hemolytic "complements," but there is supposed to be a specific complement for each specific bacterium and corresponding immune body. Such a determination is obviously impossible. In the second place if a single organism is taken to represent all possible bacterial infections the method of determining the destruction of bacteria by the plate method at arbitrary intervals is inexact, on account of the unavoidable differences in seeding the mixtures from one experiment to another, the possibility of too many organisms overwhelming the alexin from the beginning and so masking a real though inferior activity, and other uncontrolled details, which in the presence of the most careful technic are sure to occur during an experimental period extending over twenty-four hours at body temperature.

The bacteriolytic method, moreover, is laborious and precludes the determination of several control reactivating sera at the same time. While the general deductions from numerous experiments are probably in the main exact, the determination of the alexic content by bacteriolysis certainly offers no safe nor easy criterion for the determination of slight differences in the reactivating power of human blood in a given case. The employment of a normal immune body, even if the same serum be used for an entire series of experiments, is likewise inaccurate for reasons that will presently be discussed.

Moro[8] quite recently has advocated a method of determining the alexic content of human blood by means of the reactivation of a heated hemolytic immune serum active against sheep corpuscles and obtained from rabbits. No experimental data are given as to whether the arbitrary dose of corpuscles and immune serum in reality represent a fixed unit which will detect unfailingly a like alexic activity in different sera. Nor does he mention whether the relative hemolytic reactivating power of different sera corresponds to their relative power to destroy bacteria.

We have adopted, after careful experimental control, the hemolytic method of detecting quantitative variations in the alexic content of human serum on account of the greater ease and accuracy which the method affords. It was necessary first to establish a relatively unvarying unit composed of corpuscles and heated immune serum which could be readily prepared at any time and which would serve to detect precisely the same amount of alexic activity in a reactivating serum.

It is a matter of common observation by those accustomed to experiments in hemolysis that certain quantitative relations exist between corpuscles, immune serum (56°), and alexin. Certain of these relations have been concretely demonstrated by Morgenroth and Sachs,[9] who have shown among other facts that, within certain limits, the greater the amount of immune serum the less the amount of alexin necessary to produce complete hemolysis and, conversely, the greater the amount of alexin the less the amount of immune serum necessary.

When one considers that in different experiments it may be necessary to use corpuscles from different individuals of the same species, which naturally differ slightly in susceptibility, or that even if corpuscles of fixed resistance could at all times be employed, a given immune serum might change in potency or it might be necessary or convenient to use an immune serum from a different individual than the one previously employed, and that such different sera are sure to vary in potency, the necessity for establishing a hemolytic unit relatively invariable at all times is obvious. For this purpose the following experiment was performed:

Experiment I.

Several rabbits were immunized against defibrinated cow blood by injections of from one to three cubic centimeters five times, at intervals of from four to seven days, and the animals were bled to death aseptically ten to twelve days after the last injection. After clotting and standing for twenty-four hours, the separated serum from each animal was pipetted off, centrifugalized in a separate sterile tube, and the individual sera were heated to 55–56° C. for thirty minutes. Sera from three of these animals, chosen at hazard, were used in the following experiment and are designated:

Serum rabbit > cow No. 18, 56°.
“ “ > “ No. 15, 56°.
“ “ > “ No. 16, 56°.

Blood was obtained from the ear veins of three different cows, was washed twice in an excess of NaCl solution (.85

per cent) (one cubic centimeter of blood to fifty cubic centimeters of salt solution), and the sediment after the second centrifugalization was brought to a five per cent suspension by the addition of salt solution. These blood suspensions are designated A, B, and C, respectively. Mixtures of corpuscles and immune serum were then made as follows:

I. Corpuscles A 5%, 7 cc. + serum rabbit > cow No. 18, 56°, 0.7 cc.
II. “ B “ “ “ + “ “ “ “ “ “ “ “
III. “ C “ “ “ + “ “ “ “ “ “ “ “
IV. “ B “ “ “ + “ “ “ “ 15, “ 0.75 “
V. “ B “ “ “ + “ “ “ “ 16, “ “ “

These mixtures were then placed at 37° C. for two hours. The quantities of immune serum in these mixtures was chosen from previous experiments as being sufficient to saturate the amount of blood used. That the corpuscles were indeed saturated was proved by centrifugalizing the mixtures after contact and testing the supernatant fluids for uncombined hemolytic immune body, as follows:

1. Superfluid I. 1 cc. + washed cow blood A .05 cc. + human alexin * .05 cc.
2. “ II. “ “ + “ “ “ “ “ “ + “ “ “ “
3. “ III. “ “ + “ “ “ “ “ “ + “ “ “ “
4. “ IV. “ “ + “ “ “ “ “ “ + “ “ “ “
5. “ V. “ “ + “ “ “ “ “ “ + “ “ “ “
6. Washed cow blood A 5%, 1 cc. + human alexin .05 cc.
7. “ “ “ B “ “ “ + “ “ “ “
8. “ “ “ C “ “ “ + “ “ “ “

These tubes were placed at 37° C. for two hours, and then at 0° C. until the next day; readings of hemolysis were made at intervals up to two hours and also the next day.

Resultant hemolysis:

Tubes 1, 2, 3, 5 = complete 1 hour.
Tube 4 = marked “ “
Tubes 6, 7, 8 = no hemolysis next day.

The corpuscles in sediments I.–V. may then be said to be saturated, *i.e.*, to have absorbed the maximum amount of immune body, since the presence of uncombined immune body can be detected in the superfluid. The human serum used as alexin has no hemolytic activity for the cow corpuscles employed.*

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* Human serum obtained from clot and, in this case, kept for three days at 0° C.

The saturated sediments of cow corpuscles were then washed in fifty cubic centimeters of salt solution and, after centrifugalizing, the wash fluid was removed and the original volume of the corpuscles was restored (five per cent suspension). The ability of fresh human serum in various doses to hemolyze these corpuscles was then tested, the results of which are schematized in the following table:

TABLE A.

The susceptibility of corpuscles from different individuals of the same species saturated with a given specific immune serum; and the susceptibility of corpuscles from a given individual saturated with immune serum from different individuals of the same species — to hemolysis by human alexin.

Amounts of human serum made to equal in volume .1 cubic centimeter by dilution with salt solution.

1 cc. 5% suspension of	Dose of Serum and Resultant Hemolysis.				
	1/40 cc.	1/60 cc.	1/80 cc.	1/100 cc.	1/120 cc.
Saturated corpuscles I....	Complete.	Complete.	Complete.	Nearly complete.	Marked.
‘ “ II....	“	“	Nearly complete.	Nearly complete.	Slight.
“ “ III....	“	“	Complete.	Marked.	“
“ “ IV....	“	“	Nearly complete.	Slight.	“
“ “ V....	“	“	Nearly complete.	Marked.	Marked.

It is evident from these results, which correspond within very narrow limits, and present only differences attributable to experimental error, that:

1. Red blood corpuscles from different cows, saturated each with the same heated immune serum from a rabbit, are equally hemolyzed by a given dose of human alexin; and (2) the same corpuscles saturated with immune sera from

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* This is found to be true in the case of nearly all human sera tested, although in a few instances, and in larger doses, a slight hemolysis was noted. The presence of such small amounts of hemolytic immune body may, however, be neglected in the doses of alexin used in the following experiments.

different rabbits are equally hemolyzed by a given dose of human alexin.

It is evident, then, that if we employ a given amount of blood corpuscles from any cow and saturate them with immune serum obtained from any rabbit that we have at all times a relatively fixed hemolytic unit by which may be tested the reactivating activity (alexin) of different sera. It is probable that other combinations of corpuscles and immune serum may be used.

Although we have established a convenient hemolytic unit, by means of which the reactivating power of various sera may be compared, not only at a given time but at different times, it has been done on the assumption either that the hemolytic alexin is identical with the bacteriolytic alexin, or at least that it varies proportionally to it. In order to test the truth of this assumption the following experiment was performed:

Experiment II.

Corpuscles from a cow were washed and suspended in NaCl solution and then saturated with heated immune serum from the rabbit, washed again and made to a five per cent suspension; each step in this experiment, and in all subsequent experiments, following in detail the conditions noted under Experiment I. to produce saturated sensitized corpuscles. Fresh blood was drawn by means of a hollow syringe needle from the arm veins of two patients (No. 2 and No. 19), allowed to clot, and after four hours the serum was separated by centrifugalizing and the alexic activity of the two sera tested:

Table B.

The results indicate the degree of hemolysis of one cubic centimeter of a five per cent suspension of saturated sensitized cow corpuscles produced by Sera Nos. 2 and 19 in various amounts, obtained by dilution in NaCl solution so that the volume added equalled in each case .1 cubic centimeter.

	1/30 cc.	1/40 cc.	1/50 cc.	1/60 cc.	1/70 cc.	1/80 cc.
Serum No. 2..	Complete.	Complete.	Complete.	Complete.	Complete.	Nearly complete.
" " 19..	"	"	"	Nearly complete.	Marked.	Marked.

The smallest amount of serum or alexin necessary to produce complete hemolysis of the hemolytic unit is, in the case of No. 2, 1/70 of a cubic centimeter and in the case of No. 19, 1/50 cubic centimeter. It may be noted here that we have chosen the smallest amount of alexin necessary to produce complete hemolysis as a convenient unit of comparison of different sera.

At the same time was tested the reactivating power of the two sera for a bacteriolytic immune serum. We have used, as being a far more delicate method of detecting small amounts and differences in alexin, Pfeiffer's reaction in vitro as first described by Bordet.

To four twenty-four-hour agar cultures of V. choleræ Asiat. was added ten cubic centimeters of normal salt solution and a suspension made. To eight cubic centimeters of this cholera suspension was added 1.5 cubic centimeters of the serum of a rabbit immunized against cholera, which serum had been heated to 56° C., and after contact tubes were prepared as follows:

1. Emulsion sensitized cholera vibrios .5 cc. + Serum No. 2, 1/100 cc.*
2. " " " " " " + " " " 1/200 "
3. " " " " " " + " " " 1/400 "
4. " " " " " " + " " " 1/800 "
5. " " " " " " + " " 19, 1/100 "
6. " " " " " " + " " " 1/200 "
7. " " " " " " + " " " 1/400 "
8. " " " " " " + " " " 1/800 "
9. " " " " " " + NaCl .85% .5 cc.
10. " normal " " " " + Serum No. 2, 1/100 cc.
11. " " " " " " + " " 19, 1/100 "

After one and one-half hours at 37° C. smears made from each tube and stained (Toluidin blue or acid fuchsin) showed the following results:

1. Complete granular disintegration of vibrios.
2. " " " " "
3. Marked change. Numerous granular and swollen vibrios; agglutination of vibrios.
4. No distinct change. Agglutination of vibrios.

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* Dilutions made with NaCl so that each equals in volume .5 cubic centimeter.

5. Complete granular disintegration.
6. Partial change. Swollen forms; no marked granules; less than No. 3; agglutination.
7. No change. Agglutination.
8. " " "
9. " " "
10. " " No agglutination.
11. " " " "

It is evident that serum No. 2 produces bacteriolysis of sensitized vibrios in smaller amounts than serum No. 19.

This experiment, and others performed under similar conditions, showed that sera compared as to their alexic activity for the hemolytic unit show corresponding relations in their reactivation of bacteriolytic immune bodies; such relative correspondence may be taken moreover as a strong proof in favor of the unity of the alexin as maintained by Bordet. The method then of comparing alexic activities by means of hemolytic reactivation may be used as a means of comparing the relative activities in sera in the resistance to bacterial infections.

The patients, the alexic activity of whose blood we have studied, were for the most part suffering from the various forms of insanity. We had in mind in the beginning the possibility of detecting constant differences in alexic content between the different types of insanity; this possibility was rendered reasonable by the statement of Dide,[10] who asserts that there is a diminution in alexin in patients suffering from the "toxi-infectious" forms of insanity, notably Dementia præcox and General paralysis, although his method of determination of the alexin does not inspire confidence. We examined the blood of a considerable number of cases suffering from dementia præcox, general paralysis, epilepsy, senile dementia, maniac-depressive insanity (both maniac and depressed phases), alcoholic insanity, and the like, without, however, finding any constant differences in the alexin as regards the types of disease studied. The individuals studied were physically well in nearly all instances and in no case presented evidence of any acute infection. They may therefore be regarded, it seems to us, from the standpoint of recognized bacterial infection, as normal. The determinations of alexin in these cases, if we regard the alexin fluctuation as indicative of the success or failure in resistance to infectious disease, might be expected to correspond in large measure, and to be similar to that of individuals both physically and mentally normal.

We offer, then, a table of the alexic activity in various cases of physically well insane patients, not as having any particular relation to insanity, but as establishing a mean of the normal human alexic activity. No especial reference is made, then, as to the type of insanity from which the patient was suffering. The table is further illustrative, on account of the number of cases which correspond in alexic dosage, and on account of the instances in which two or more estimations were made on the same individual, of the accuracy of our method for determining alexin.

The patients whose blood was tested were bled, largely for accuracy in establishing the method, from the arm vein with careful attention to asepsis, by means of a hollow irido-platinum needle. From five to twenty cubic centimeters of blood is thus easily obtained. After clotting at room temperature the blood was placed at 0° C. and the serum was removed in from five to twenty-four hours; the determinations here given represent the alexic activity during that period, during which time comparative tests assured us that no great variation occurs. Further notes on the effect of time on alexin formation will be given presently. Dilutions of each serum were made in salt solution in such a manner that .1 cubic centimeter contained amounts of serum varying from 1/20 to 1/100 cubic centimeter. These dilutions (.1 cubic centimeter) were added to the hemolytic unit, that is, one cubic centimeter of a five per cent suspension of saturated cow corpuscles freshly prepared for each set of cases.

Tables were constructed as in Experiments I. and II., but in the comparison here given only the completely activating dose of alexin is given as explained under Experiment II.

Other details of technic, which have already been explained, were uniformly maintained.

TABLE C.

The complete reactivating dose of human serum from cases of insanity, for a hemolytic unit of saturated cow corpuscles.

No. of Case.	Sex.	I. Determination Complete Dose of Alexin.	Date.	II. Determination Complete Dose of Alexin.	Date.
1	Male.	1/40 cc.	July 25.		
2	"	1/70 "	"	1/70 cc.	Sept. 2.
3	"	1/70 "	"		
4	"	1/40 "	"		
5	"	1/80 "	"		
6	"	1/60 "	July 31.		
7	"	1/60 "	"		
8	"	1/40 "	"		
9	"	1/40 "	"		
10	"	1/40 "	"		
11	"	1/40 "	"		
13	"	1/50 "	Aug. 3.		
14	"	1/40 "	"		
15	"	1/60 "	"		

TABLE C.—*Continued.*

No.	Sex.	I. Determination Complete Dose of Alexin.	Date.	II. Determination Complete Dose of Alexin.	Date.	III. Determination Complete Dose of Alexin.	Date.
16	Male.	1/30 cc.	Aug. 3.				
17	"	1/50 "	"				
18	"	1/30 "	"				
19	"	1/30 "	"	1/50 cc.	Sept. 2.		
20	"	1/40 "	Aug. 7.				
21	"	1/40 "	"				
22	"	1/50 "	"				
23	"	1/40 "	"				
24	"	1/40 "	"				
25	"	1/40 "	"				
26	"	1/30 "	"				
27	"	1/50 "	"				
28*	"	1/30 "	"				
A*	"	1/60 "	Oct. 28.				
29*	Female.	1/50 "	June 24.				
30	"	1/40 "	Aug. 13.	1/30	Aug. 21.		
31	"	1/10 "	"				
32	"	1/10 "	"				
33	"	1/10 "	"	1/20	"	1/20 cc.	Sept. 3.
34	"	1/30 "	"	1/20	"		
35	"	1/10 "	"	1/20	"		
36	"	1/30 "	"				
37	"	1/10 "	Aug. 21.	1/20	Sept. 3.		
38	"	1/10 "	"	1/10	"		
39	"	1/30 "	"				
40	"	1/10 "	Sept. 3.				
41	"	1/50 "	"				

* Not insane.

Summarized this table gives:

Males: Cases examined 28.*	Alexic activity	1/10 cc.	1 case.
		1/30 "	5 cases.
		1/40 "	11 "
		1/50 "	4 "
		1/60 "	4 "
		1/70 "	2 "
		1/80 "	1 case.
Females: Cases examined 13.	Alexic activity	1/10 cc.	7 cases.
		1/30 "	3 "
		1/40 "	1 case.
		1/50 "	2 cases.

It would seem that in males the normal average dose of alexin is about 1/40 cubic centimeter, while in women it is apparently lower, although a greater number of cases would be necessary to determine this difference.

As was stated the alexic determinations here recorded were made in sera removed in from four to twenty-four hours after clotting, and in the case of the longer intervals the tubes were kept for a greater part of the time at 0° C. It was found from a number of comparative tests of the same serum that no great change in the alexin occurs during this interval, although, if anything, the alexin during the later hours was somewhat more potent. Further observations showed that distinct increase in alexin had taken place if the serum at 0° C. was left on the clot for forty-eight hours, and that later a gradual decrease occurred. These observations agree with those of Walker,[11] in the main, and were deemed worthy of more careful control.

Experiment III.

Patients No. 2 and No. 19, chosen as presenting alexic activity of different intensity, were bled each into several separate tubes. After clotting and remaining four hours at room temperature the first test was made of alexic activity. The remaining tubes were placed at 0° C., and at intervals the serum was pipetted off from an undisturbed tube from each case and tested with the hemolytic unit of sensitized corpuscles. The smallest amount of serum necessary to reactivate at different intervals is schematized in

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* Cases in which more than one determination was made are counted only once.

TABLE D.

Time of removal from clot.

Alexic Activity.	4 Hours.	24 Hours.	48 Hours.	72 Hours.
Serum No. 2........	1/70	1/70	1/80	1/70
" " 19........	1/50	1/40–1/50	1/60	1/60

The slight increase of alexic activity of serum which has remained on the clot after twenty-four hours corresponds with the conception of the origin of alexin from disintegration of leucocytes maintained by Metchnikoff and by Bordet and Gengou. Further observations which tend to confirm this origin will be noted in the following article.

The material at our disposal has offered very few opportunities for observation as to the change which may occur in the alexic content of the blood in acute conditions. From the fragmentary results in our records, however, it is clear that marked divergence from the normal alexin content may occur in febrile conditions, but the relation of such changes to condition, leucocytosis, and prognosis is as yet only suggestive. Before any conclusion can be arrived at as to the value of alexin determination it will be necessary to make numerous comparative tests of the serum in health and disease, tests arranged first of all to indicate at what period after clotting divergence in alexin from the normal is most evident; although estimations of the normal alexic content have been given on the basis of serum kept for twenty-four hours or under at 0° Centigrade, it by no means follows that this set of conditions is best fitted to show divergence of alexic activity in disease; on the contrary our results would lead us to think that a greater difference is evident later (48 hours at 0° C.)

CONCLUSIONS.

1. As a relatively fixed unit for the determination of the alexic activity of human blood serum, one cubic centimeter ension of blood corpuscles from any cow saturated with (*i.e.*, which have absorbed the maximum amount of) the inactivated (56°) serum of any rabbit immunized against cow blood may be employed.

2. Differences in the alexic content of two sera, as determined by means of this hemolytic unit, correspond to differences obtained in reactivating a bacteriolytic immune body (Pfeiffer's phenomenon). The method then may properly be used as indicative of the resistance of the reactivating serum in bacteria. This fact of correspondence between bacteriolytic and hemolytic reactivation incidentally may be used as an argument for the unity of the alexin.

3. An increase in the alexic content of human serum which has remained on the clot takes place at 0° C. after twenty-four hours, which corresponds, in all probability, to the disintegration of leucocytes.

4. In a number of cases of insanity, normal as regards acute physical condition, the alexic activity of the serum as determined by this method was found to correspond very closely in the majority of cases both from one individual to another, and in several determinations made at different times on the same individual. The alexic activity of women was apparently of lower mean average than men.

No constant differences of alexic activity were noted in relation to types of insanity.

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The Journal of Medical Research, Vol. XVII., No. 3, December, 1907.

ALEXIC ACTIVITY OF THE BLOOD SERUM OF CADAVERS.*

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In the preceding article† is described a method for detecting variations in the alexin (complement) of human blood serum.

It was found that the red blood corpuscles of any cow when saturated with inactivated immune serum from any rabbit, immunized against cow blood, offered in a given volume (one cubic centimeter of a five per cent suspension) a relatively invariable hemolytic unit which will detect very delicate differences in the reactivating power of fresh human serum. It was shown, moreover, that variations from serum to serum in respect to this hemolytic alexin (reactivating serum) show corresponding relative differences in the reactivation of a bacteriolytic immune body; the employment of this hemolytic unit may therefore properly be used as an indication of the resistance of the individual to bacteria, in so far as the determination of alexin is indicative of such a resistance.

There were further mentioned certain observations which would indicate that the alexin, at least in part, is due to the disintegration of leucocytes in the blood clot, since the alexic power of serum in contact with the clot is found to increase between twenty-four and forty-eight hours. Further indication as to this increase is given in the present paper.

So far as I am aware no systematic observations are on record as to the presence or amount of the alexin in the blood serum of human cadavers. Perkins and Pay[1] do record alexic determination in one or two cases of variola very soon after death. The fact that little attention has

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* Work facilitated by a grant from the Proctor Fund of Harvard University. Received for publication Nov. 6, 1907.

† This journal, page 341.

been paid to this subject may be due perhaps to the conception that the alexin is correlative with some vital function.

In the following table are schematized the results of the alexic determination of the blood serum in cadavers which were autopsied at the Danvers Insane Hospital at various periods of time after death. The blood was taken aseptically from the right auricle, allowed to clot, or, if clotted, the serum left to rise and then freed from cells by centrifugalization. With clear, though frequently blood tinged, serum, dilutions were made in the manner which has been described and the smallest dose necessary completely to hemolyze one cubic centimeter of saturated sensitized cow corpuscles was determined. At the time of removal from the body cultures were also made from the heart's blood by means of agar plates (one cubic centimeter of blood to ten cubic centimeters of fluid agar). The bacteriological diagnosis is recorded in the last column of the table. The cadavers were admirably preserved by means of an ammonia refrigerating plant at a temperature close to 0° Centigrade in which they are placed soon after death. It has been found as the result of bacteriological examinations of the heart's blood in over one hundred of these cases that no evident increase of bacteria takes place after death at this temperature, as was estimated from the fact that there is as large a proportion of cases which give sterile cultures when examined three or four, or even six, days after death, as when autopsied within the first six hours.

TABLE A.

The alexic activity of blood serum in human cadavers.

(Dilutions of serum were made to represent only .1, .05, .02, .01, .005, and .004 of a cubic centimeter of whole serum. The smallest dose of alexin therefore given as producing complete hemolysis of the hemolytic unit* is only approximately determined.)

Autopsy No.	Hours P.M.	Minimal Alexic Dose.	Bacteriology.
1175	4	.1 cc.	Many colonies B. coli.
1181	6	.02 “	“ “ Streptococcus.
1185*	6	.01 “	“ “ B. coli.
1171	10	.01 “	Sterile.
1197	15	.01 “	Many colonies M. pyogenes albus.
1184	15	.005 “	Few “ “ “ “
1166	17	.1 “	Many “ B. coli.
1162	20	.01 “	Sterile.
1183	20	.01 “	Many colonies B. coli.
1191	20	.005 “	Numerous colonies M. pyogenes albus.
1178	27	.01 “	Sterile.
1193	30	.05 “	“
1180	41	.05 “	“
1174	45	.02 “	“
1190	48	.02 “	Numerous colonies M. pyogenes albus.
1199	48	.005 “	Contaminated.
1195	59	.02	Sterile.
1188	60	.02 “	Many colonies M. pyogenes albus.
1182	69	.01 “	Sterile.
1203	70	.02 “	No culture.
1165	144	.1 “	Sterile.

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* As additional control it was proved that blood serum No. 1185 would also complete bacteriolysis of sensitized cholera vibrios in high dilutions (.01 cubic centimeter). See preceding paper.

Several conclusions may be drawn from this table :

1. Alexin is uniformly present in the blood serum of cadavers and it shows no marked decrease for at least three days when the bodies are kept at 0° C.

2. In comparison with the tables of alexic activity in living human beings, as shown in the previous article, the alexic activity in cadavers is relatively higher, a fact which may be correlated with a more rapid and complete disintegration of leucocytes after death.

3. The presence or absence of bacteria in the heart's blood after death produces no notable change in the alexic content of the blood. But the alexin, it will be remembered, cannot unite with an immune body-cell complex at 0° C. even in the case that suitable normal immune bodies are present.

These results in reality throw little light on whether or not the alexin has been diminished before death, as it might subsequently be increased ; and for this reason they give little information as to whether bacteria present in the blood post-mortem are due to ante-mortem or post-mortem invasion.

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